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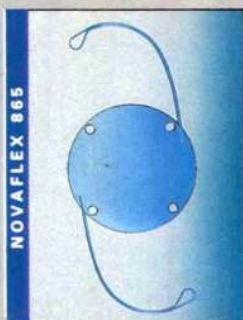
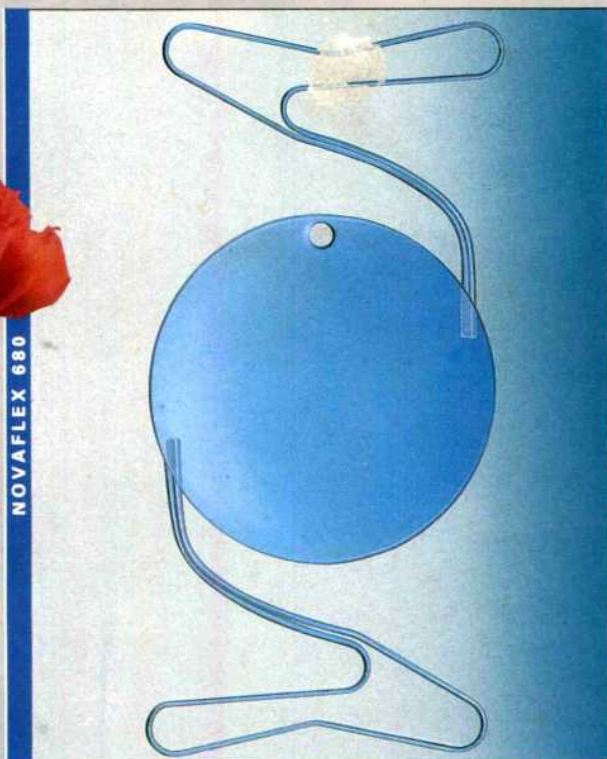
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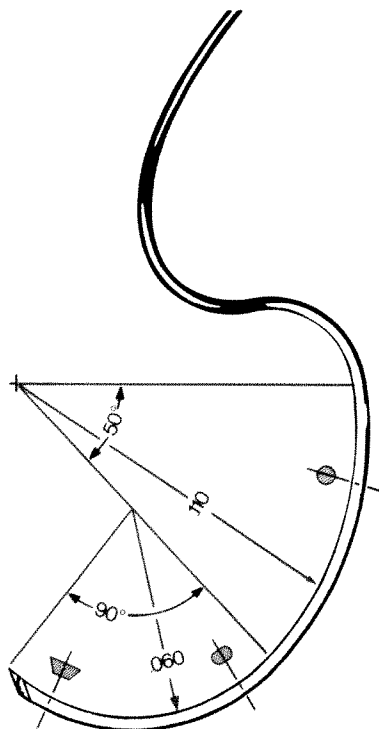
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Editorial: An Enigma Variation

The progressive loss of field which occurs in chronic glaucoma has been widely assumed hitherto to be due to raised intraocular pressure (IOP). For example, Duke-Elder and Jay stated¹: 'It is undoubtedly true that the defects in the field are generally related to the height of the tension....' The statement is not, however, supported by a reference, a surprising omission in a work of the calibre from which the quotation is taken.

The first long-term prospective study of the relationship between IOP and field on a quantitative basis was reported on in 1968,² though other authors had attempted to study the problem but without scoring the fields in a numerical form suitable for statistical analysis.^{3,4} None of these publications were able to show incontrovertible evidence of a relationship between pressure and field loss, but a later publication⁵ indicated that there might be an association between field loss and peaks of IOP rather than higher average values, and still further evidence of a weak association was forthcoming in the Lang Lecture in 1986.⁶ However, in the meantime Krakau, using a sophisticated system of scoring 'decay' of field was casting serious doubt on the cause-effect relationship between IOP and field decay.⁷

In the present issue we have a paper from the Vancouver group which comes to the startling conclusion that there is a negative correlation between IOP and 'scotoma mass.' The follow-up in this (retrospective) study appears to have been relatively short, but nevertheless it would seem fair to assume that the scotoma mass would tend to increase with time (though the paper makes no categorical statement to that effect).

This leads us to an amazing conclusion. If the average IOP for the 2-3 readings before and the one at the time of perimetry are negatively correlated with scotoma mass, and if the scotoma mass increases

with time, then there seems to be no way of avoiding the conclusion that the IOP should decrease with time. Unfortunately this information is not separately presented in the study, though there is one figure suggesting that the majority of patients did indeed have a negative IOP time slope.

What can we conclude from this? At this stage not very much, but one legitimate speculation is possible. If the patients were under treatment, it is possible that the majority might well have a negative IOP time slope because of the treatment. But this unfortunately does not tell us if the treatment was doing anything so far as the field was concerned. In a different group with a flat IOP time slope it might have been found that increase in scotoma mass was even greater. There are of course further problems in sampling where the very variable results of attempts to quantitate visual fields are concerned – as Krakau has recently warned.⁸ Thus the enigma of pressure in its relationship to field loss is still very much with us and looks likely to remain so for some time to come.

REDMOND JH SMITH

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Some observations on the relation between intraocular pressure reduction and the progression of glaucomatous visual loss

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SUMMARY A quantitative measure of visual field loss associated with kinetic perimetry in chronic open-angle glaucoma (COAG) is discussed. With this new technique an analysis of covariance is applied to a retrospective study of 41 COAG patients. It suggests that reduction of intraocular pressure may not be uniformly effective in controlling the progression of the disease.

When the visual fields of a patient with chronic open-angle glaucoma are determined by kinetic perimetry, they show considerable variation with time in the number of scotomas, their size, and density. It is therefore not an easy matter to assess the progression of the disease in a given eye over successive perimetric examinations. Thus the efficacy of treatment is difficult to establish, and only marked changes in the visual field can be noted.

It was our aim to try to develop, on the basis of manual perimetric measurements, a reasonable quantitative summary which might be representative, specific, and consistent in its assessment of the patient's visual field. This quantification method of the 'scotoma mass' has been fully described by us elsewhere.^{1,2}

Materials and methods

A retrospective sample of 41 eyes of 41 patients with chronic open-angle glaucoma was obtained by reviewing computerised records which were readily available.^{1,2} To qualify for inclusion in this sample the eyes had to have paracentral or arcuate defects within the central 30° as well as two or more years of follow-up after the development of visual field defects. There were 23 men and 18 women. Their median age at the start of the study was 61.75 years (first quartile

55.75, third quartile 68.25), and median follow-up time was 96 months (first quartile 49.5, third quartile 120).

The visual fields were recorded with the Tübinger perimeter by both kinetic and static techniques. Only patients whose initial visual acuity was 6/9 or better and those whose final visual acuity was 6/12 or better were studied. By means of this cut-off the amount of extraneous change was minimised. The Zeiss video plan was used to measure by planimetry the areas of the scotomas within the central 30°. On each eye a large set of observations was available over time, consisting of multiple manual perimetric determinations by experienced technicians, numerous intraocular pressure (IOP) determinations interspersed throughout the follow-up period, visual acuity measurements, details of treatment, and other data.

The sequence of stimulus strengths used in our study to explore the scotomas was 10, 16, 32, 64, 100, 320, 640, and 1000 apostilb, with a 10-minute size target on a 10-apostilb background. Since the brain tends to perceive intensity changes logarithmically,³ as well as for statistical validity, stimulus intensities were re-expressed in log-apostilb (= 'decibel') units.

The total mass of all excavations (scotomas) identified as glaucomatous was evaluated as described.² This yielded a final quantity M , in $\text{mm}^2 \times \text{decibel}$ units, which measured the total visual loss due to scotomas ('scotoma mass') at a given time. It increased with the number of scotomas, with their traditionally measured areas to specific stimulus

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intensities, and with their depths in terms of the logarithm of the stimulus intensities used to identify them. It was found to outperform these univariate measures (number of scotomas, traditional areas, intensities) in terms of its longitudinal correlation with time, continuous availability of information over time (individual scotomas can usually be followed for a limited time only and thus continuity is lost), and a continuous range of values (unlike, for example, the discrete count of the number of scotomas).

Results

The relationship between scotoma mass and the intraocular pressure was examined in the 41 patients. Between any two successive perimetric determinations of the visual field a number of intraocular pressure readings were available. The means and standard deviations of these sets of readings were obtained, as well as the maximum intraocular pressure observed during such a period. By means of analysis of covariance⁴ the regression of scotoma mass was determined longitudinally (within patients) on the mean intraocular pressure recorded over the period just prior to the given perimetric determination. A highly significant negative correlation was observed between these two quantities ($p=0.003$). Low mean IOP values tended to correspond to high values of scotoma mass (Fig. 1).

A similar negative relationship was found between the scotoma mass and the maximum IOP reading in the preceding time interval. No correlation

was observed between the scotoma mass and the logarithm of the standard deviation of the IOP readings ($p=0.72$).

The longitudinal regressions of mean IOP on time indicated significant negative slopes ($p=0.00005$), with considerable interpatient variation.

The slope of scotoma mass over time for each patient was examined against the corresponding mean IOP time slope (Fig. 2). No significant correlation was found ($p=0.42$).

Discussion

Specific quantitation of glaucomatous visual loss has been difficult in ophthalmological practice until the recent advent of automatic perimetry.^{3a} We developed a single, quantitative assessment of the total 'mass' of glaucomatous field loss. It represents, essentially, the sum of products of areas of scotomas in the inner 30° of the field by their depths, where depths represent the logarithm of corresponding stimulus intensities used to explore the scotomas.

Our study of this scotoma mass measurement suggests that it possesses desirable statistical properties (symmetric distribution with light tails), which permit the use of standard analytical tools with reasonable validity.

The relationship between the scotoma mass and the IOP was explored. A strong, highly significant, consistent negative correlation was found between the mass of the scotomas and the IOP in the longitudinal analysis. For no patients could a positive correlation be found between the scotoma mass and

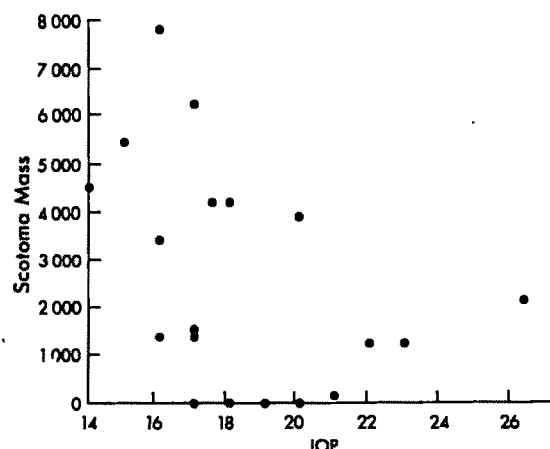


Fig. 1 Example of the correlation between intraocular pressure and total scotoma mass in one of the patients. The individual points are presented according to pressure level but independently of time. The scotoma mass and the intraocular pressure show a great variation, and there is a negative correlation between them.

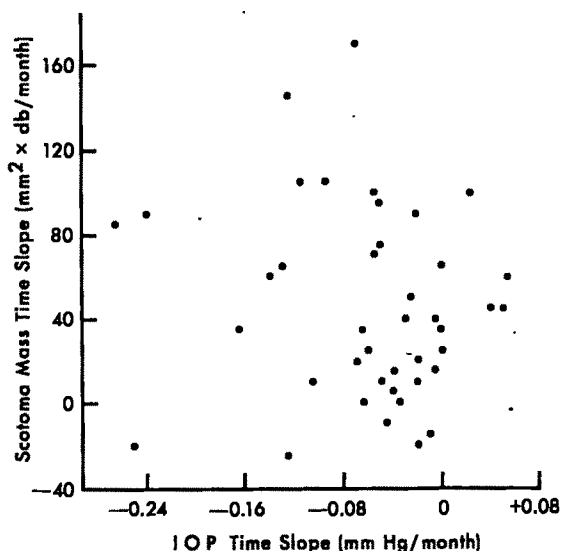


Fig. 2 Scatterplot of scotoma mass time slope for each patient against the corresponding IOP mean time-slope.

the IOP. In the only other major study on progression Hart and Becker⁷ also found no correlation between IOP and the course of glaucomatous visual field defects.

Our data must be interpreted with caution. The sampling method excluded patients whose follow-up was too short (less than two years), and it was focused in the main on progressive cases. Extrapolation outside these limits should be avoided. Moreover, it is likely that in the management of these patients it was decided to treat the pressure more vigorously if it appeared to have been too high. One would also be inclined to respond more aggressively if the visual field loss had progressed. These factors may affect the relationship between the scotoma mass rate and IOP rate. However, the finding that the mass rates of change and the IOP rates of change were in fact independent may obviate this difficulty.

It is also possible that, as the disease advances and the scotoma mass increases, a natural burn-out can occur in some cases, which results in a pressure reduction with time. The pre-eminence of the role of IOP in glaucoma has recently been questioned by Krakau *et al.*⁸ Our data showed no positive pressure-mass correlations. Only a carefully designed, pro-

spective study could help untangle the correct interpretation of this finding. The recent computerisation of perimetry will make this task much easier.

This work was supported in part by MRC grant MT-1578 and the E A Baker Foundation for the Prevention of Blindness.

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A comparison of Goldmann and Humphrey automated perimetry in patients with glaucoma

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SUMMARY Humphrey automated threshold perimetry (Program 30-2) was performed on 42 eyes of 25 patients with glaucoma to determine both the sensitivity and specificity of automated perimetry in detecting glaucomatous visual field defects. Automated perimetry sensitivity was 90.38%, while automated perimetry specificity was 91%. Fifty-two patients and a technician took part in a survey to determine their preference for either test. Patients generally preferred having Goldmann perimetry. The technician favoured Humphrey automated perimetry. Program 30-2 on the automated perimeter took 25% longer to perform than Goldmann perimetry.

There are a number of automated perimeters on the market. These computerised perimeters all perform visual field tests using preprogrammed and/or programmable test logics. Some of these perimeters can determine retinal threshold sensitivity, and their performance in patients with glaucoma has been favourably compared to that of standard, manual perimetry (Fig. 1).¹

The Humphrey automated perimeter is a new and relatively inexpensive automated perimeter that can perform both relatively rapid suprathreshold static perimetry for glaucoma screening and threshold static perimetry. Threshold perimetry allows for quantification and therefore follow-up of patients with glaucomatous visual field defects. Recent reports have indicated that the Humphrey perimeter can be favourably compared with conventional manual perimeters.^{2,3} We are not, however, aware of studies comparing the sensitivity and specificity of this automated perimeter with standard Goldmann perimetry in patients with glaucoma.

The purpose of this study was two-fold. First we wished to determine patient and technician preference for either machine. Secondly, we wished to determine the sensitivity and specificity of Humphrey automated perimetry using the Goldmann perimeter as standard in patients with glaucoma.

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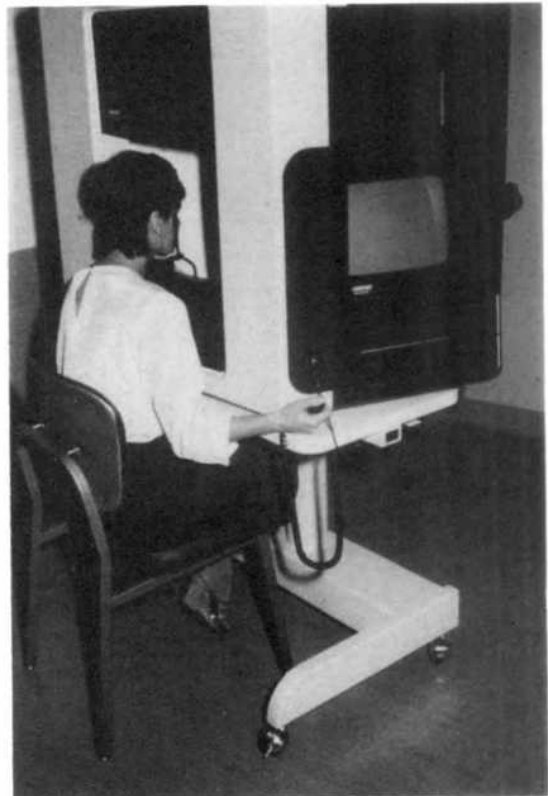


Fig. 1 Humphrey automated perimetry.

performed with Program 30-2. This program tests the central 30° field at 76 points. Points tested are 6° apart. Initially, this automated perimeter determines retinal threshold at four primary points—i.e., one in each quadrant 10° from fixation. It does so by presenting a stimulus which is very bright (supra-threshold). The intensity is then reduced in 4 db decrements until it is not seen. The stimulus then increases in 2 db increments until it is seen again. This value is recorded as the patient's retinal threshold. The four initial thresholds are then used as starting points to determine the thresholds of neighbouring points by means of the same bracketing technique. These points are used in a similar manner to determine retinal thresholds of neighbouring points until the central 30° area has been fully tested. If a value varies from expected by more than 4 db, it is remeasured automatically.

The Humphrey automated perimeter Program 30-2 uses a background illumination of 31.5 apostilbs with a 4 mm² stimulus size (equivalent to Goldmann perimeter size III target); the appropriate near correction for age is used.

The nasal step was not tested in this study as the nasal step program had not yet been installed in the perimeter. Fixation is monitored both by the technician and indirectly by the machine.

The blind spot is located at the beginning of the test, and during the test approximately 10% of the stimuli are presented in the blind spot. If fixation is accurate, the patient will not see any of the stimuli presented in the region of the blind spot. If the patient responds that he does see a significant number of stimuli presented to the blind spot, a beeping sound is emitted by the machine to alert the technician to encourage patient fixation. The number of times fixation is lost is typed out on the result sheet. The test continues to run even if fixation is very poor.

The machine also assesses patient reliability by occasionally producing just the sound associated with the light stimulus without actually presenting the light. If the patient responds to this sound, by pressing the response button, this is considered a false positive result. Periodically a suprathreshold stimulus is presented to the patient that he/she should easily see. If the patient fails to respond, this indicates lack of attention, a false negative result. Fixation loss and false positives and negatives are all printed out on the visual field chart together with a grey scale, decibel scale, and a scale that indicates deviation of retinal threshold from expected decibel values (Fig. 2).

ANALYSIS OF VISUAL FIELDS

For part 2 of this study (sensitivity and specificity) we used decibel criteria modified from papers published

by Heijl and Drance.¹⁵ The criteria for abnormality with the Humphrey automated perimeter were: (1) All peripheral test points were excluded to avoid lens rim artefact. (2) Test points immediately above and below the blind spot were excluded. (3) A 5 db difference between two neighbouring points in conjunction with a 10 db difference in mirror image points between the upper and lower hemifield were considered positive glaucoma visual field defects. (4) One or more points 15 db below the point of highest retinal sensitivity was considered an abnormal visual field.

Sensitivity and specificity results were analysed according to standard methods.⁶ The sensitivity of Humphrey automated perimetry was defined as the number of abnormal Humphrey visual fields divided by the number of Goldmann abnormal visual fields expressed as a percentage. Humphrey automated perimetry specificity was determined by dividing the number of normal Humphrey automated perimetry fields by the number of normal Goldmann visual fields expressed as a percentage.

Results

Part 1. Table 1 reviews the results of the patients surveyed. Sixty per cent of the patients preferred Goldmann perimetry. Patients generally thought fixation was easier to maintain with the Goldmann perimeter. Fifty four per cent of patients, however, had previously had a Goldmann visual field test. None of the patients had previously undergone automated visual field testing.

Table 2 reviews the results of the technician survey. Fixation appeared to be similar to the technician during both of the tests. The technician found automated perimetry overall a little easier to perform than Goldmann perimetry. Technician preference strongly favoured Humphrey perimetry.

The mean test time for both eyes was 26.2 minutes

Table 1 *Fifty-two patient responses*

	Goldmann	Humphrey	Same
Patient preference	60%	17%	23%
Fixation ease	44%	21%	35%
Previous field test	54%	0%	—

Table 2 *Technician survey*

	Goldmann	Humphrey	Same
Fixation	15%	15%	70%
Technical ease	10%	40%	50%
Preference	13%	67%	20%

Table 3 Sensitivity and specificity of Humphrey perimetry using Goldmann perimetry as standard

Humphrey automated perimetry sensitivity:

$$\frac{28}{31} \times \frac{100}{1} = 90.3\%$$

Humphrey automated perimetry specificity:

$$\frac{10}{11} \times \frac{100}{1} = 91\%$$

for Goldmann perimetry and 32.6 minutes for automated perimetry.

Part 2. Table 3 reviews the sensitivity and specificity of Humphrey automated perimetry Program 32.

Sensitivity tests showed that the Humphrey automated perimeter detected 28 abnormal glaucomatous visual fields out of a total of 31 abnormal fields (90.3%). Specificity tests showed that there

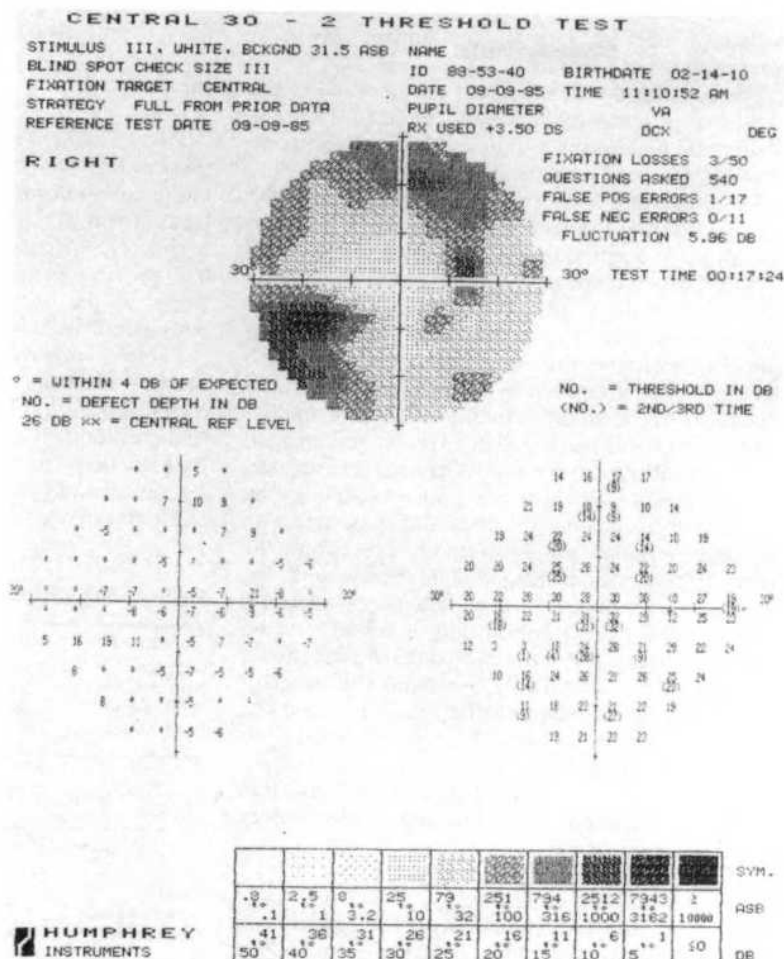
were 10 normal Humphrey fields compared with 11 normal Goldmann fields (91%).

Discussion

The major purpose of this study was to determine the sensitivity and specificity of Humphrey automated perimetry to detect glaucomatous visual field defects using the Goldmann perimeter as the standard. The results of this section of the study indicate that Program 30-2 is both highly sensitive and specific for detecting glaucomatous visual field defects. The sensitivity and specificity results reported here are similar to those reported for the Octopus perimeter using Tübinger perimetry as the standard.¹

Although the Humphrey automated perimeter is both sensitive and specific for glaucomatous visual field defects, it does have various drawbacks when compared with Goldmann perimetry. Firstly, auto-

Fig. 3 An abnormal Humphrey visual field.



mated perimetry takes about 25% longer to perform than Goldmann manual perimetry. Further, patients clearly prefer Goldmann perimetry to automated perimetry, but this preference may be biased by the fact that nearly half the patients had previously undergone only Goldmann perimetry. The prolonged test time, the rapid appearance and disappearance of the light stimulus, and the fact that the test continues to run despite detection of poor fixation suggest to us that this automated perimeter in no way overcomes many of the major obstacles to accurate visual field assessment such as accurate fixation, maintenance of concentration, and patient fatigue. A major advantage of the Humphrey automated perimeter, however, is that it can be performed by less highly trained technicians. It also overcomes the tedium of manual perimetry, and operator error is completely avoided.⁵

It is important to note that the use of only Program 30-2 on the Humphrey automated perimeter, although highly sensitive and specific for glaucomatous visual field defects, will not detect visual field defects close to fixation nor in the nasal step area beyond 30°. Furthermore, it will not detect defects between the 76 points tested in the central 30° (Fig. 3). The machine does, however, have a separate program to test the nasal step area and a macular threshold program to test the visual field close to

fixation. Static profiles can also be tested. Other programs also exist which allow one to test areas not tested by Program 30-2. Clearly, however, the use of Program 30-2 with one or more of these other test programs will add significantly to the already fairly lengthy test period. These combined programs will, however, allow for very accurate assessment of the visual field in glaucoma.

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Postural response of intraocular pressure in chronic open-angle glaucoma following trabeculectomy

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SUMMARY Forty-six eyes with chronic open-angle glaucoma (COAG) and 24 eyes which had previously undergone trabeculectomy for COAG were studied and the postural response of the intraocular pressure compared with that of 70 normal eyes. In all three groups the greatest rise in intraocular pressure (IOP) occurred when the subject changed from the sitting to the lying position. In the control group this was never more than 2 mmHg in any subject. The rise was greater than 2 mmHg in 93% of the patients suffering from COAG who were treated medically and in 100% of the eyes of those on which trabeculectomy had been performed. The well recognised abnormal postural response of intraocular pressure in COAG appears both to be retained and to be unaffected in those eyes which have undergone trabeculectomy.

An abnormal postural response of the intraocular pressure (IOP) is well known in patients with chronic open-angle glaucoma (COAG)^{1,3} and associated disorders such as retinal vein occlusion^{4,5} and ocular hypertension.⁶ An abnormal postural response of IOP in eyes which had suffered a traumatic hyphaema has also been described.⁷

Trabeculectomy is a well established method of surgical treatment of COAG.⁸ We studied the postural intraocular pressure response in patients with COAG to determine whether or not an abnormal response was retained after this operation.

Materials and methods

Thirty-five patients attending for outpatient treatment of chronic open-angle glaucoma at Southampton Eye Hospital were examined. Twenty of these patients had received medical therapy only for control of their glaucoma. They had a mean age of 69.8 years (range 52 to 85 years), there being 11 males and nine females. The other 15 patients (seven males and eight females) had undergone a trabeculectomy operation within six years of the current examination, though no account was taken of the time elapsing between surgery and the examination. Nine of these 15 patients had undergone bilateral trabeculectomy and had a mean age of 70.6 years (range 52 to 81 years). The other six patients had undergone

unilateral trabeculectomy and had a mean age of 73.0 years (range 58 to 85 years). The criteria for the diagnosis of COAG to be made in all patients included all the following features: untreated IOP greater than 21 mmHg by Goldman applanation tonometry, glaucomatous cupping of the optic disc, characteristic glaucomatous visual field defects, and gonioscopically open anterior chamber angles.

A series of 35 control patients (70 eyes) was also examined. Sixteen of these patients were male, 19 were female. The mean age of the patients was 72.6 years (range 65 to 87 years). These patients were being followed up in the outpatient department for the progression of early cataracts. All had routine applanation tonometry and examination of the optic discs to exclude COAG.

No account was taken of the use of either topical or systemic drug therapy in any case.

All intraocular pressure measurements were taken as an average of two 10-second recordings with an Alcon Applanation Pneumotonograph which had been recently calibrated. The required posture was assumed for 10 minutes before each pressure measurement, and recordings were made in the following postures consecutively: standing, sitting, and lying. The right eye was always examined first.

Results

The mean intraocular pressures of the four groups in the three positions are shown in Table 1 and are illustrated in Fig. 1.

* Work undertaken during fourth year medical student elective. Correspondence to Mr S J Keightley, FRCS, Southampton Eye Hospital, Wilton Avenue, Southampton SO9 4XW.

Table 1 Mean (standard error) intraocular pressures in mmHg

Position		Standing	Sitting	Lying
Unoperated COAG (40 eyes)	Left	18.8 (0.59)	19.1 (0.64)	23.3 (0.65)
	Right	19.2 (0.82)	19.5 (0.79)	24.0 (0.72)
Unilateral Trabeculectomy (6 eyes)		17.0 (1.23)	17.7 (1.65)	22.0 (1.76)
Contralateral Unoperated eyes (6 eyes)		20.7 (1.82)	20.7 (1.42)	22.4 (1.55) *24.8 (see text)
Bilateral Trabeculectomy (18 eyes)	Left	16.4 (0.60)	15.7 (0.62)	21.2 (0.47)
	Right	16.2 (0.49)	15.6 (0.77)	21.6 (0.22)
Controls (70 eyes)	Left	14.4 (0.24)	14.8 (0.18)	15.7 (0.32)
	Right	14.4 (0.20)	14.7 (0.22)	15.6 (0.22)

The greatest rise in IOP occurred on changing from the sitting to the lying position in all groups. No eye in the control group showed a rise of more than 2 mmHg. However, all but two (separate patients) of

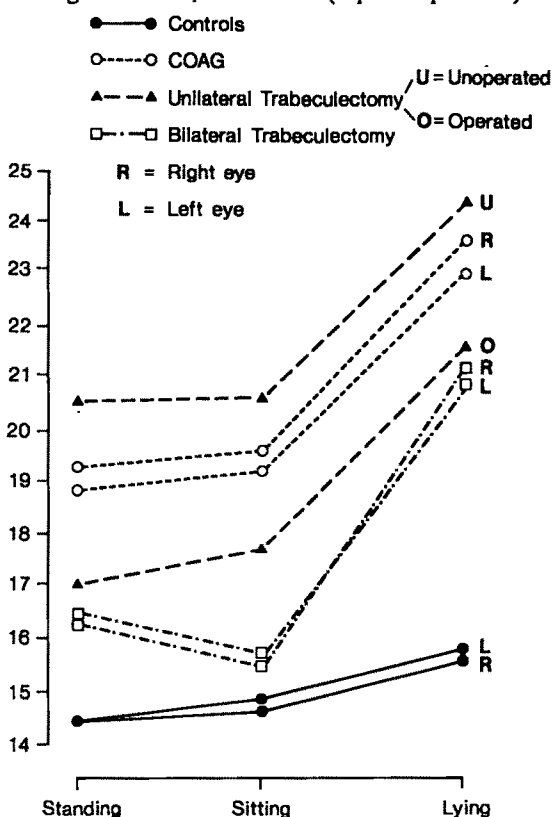


Fig. 1 Mean intraocular pressures of the four groups of patients in different postures.

the 40 unoperated glaucomatous eyes had a rise in IOP greater than 2 mmHg. All 18 eyes in the bilateral trabeculectomy group and all six in the unilateral trabeculectomy group had a rise greater than 2 mmHg on changing from the sitting to the lying position. Five out of the six contralateral unoperated eyes similarly had a rise greater than 2 mmHg. However, the sixth unoperated eye had a fall of 7.5 mmHg, the IOP being recorded as 17.5 mmHg in the lying position. This IOP value was very low (standardised value 3.48) and appears to be erroneous. Analysis confirms that this response was significantly different from the overall pattern ($p < 0.001$). A reanalysis, treating this value as missing, produced a much more coherent pattern of results and is to be preferred. The asterisk * in Table 1 denotes the mean IOP value in the lying position when this very low value is considered missing in the unoperated group of eyes.

There was no significant difference in postural response of IOP by age or sex (observed $F_{66}^3 = 0.61$, $p > 0.05$), and the difference between the IOPs in the standing and sitting positions was also not significant (observed $F_{132}^1 = 0.04$, $p > 0.05$).

However, there was a significant difference between the mean standing/sitting position and the lying pressure in all patient groups (observed $F_{132}^1 = 377.1$, $p > 0.01$). There was also a significant difference in the amount of pressure change between groups (observed $F_{132}^3 = 4.39$, $p < 0.01$). The rank order of these pressure rises was bilateral trabeculectomy 5.46 mmHg, medically treated glaucoma 4.43 mmHg, unilateral trabeculectomy 3.31 mmHg, and controls 1.08 mmHg.

Discussion

Anderson and Grant² provided data on the effect of different methods of treating COAG on the postural intraocular pressure response. Their results showed a mean IOP rise of 2.83 mmHg in eyes treated by surgery on changing from the sitting to the lying position. Groups of eyes receiving various medical treatments had a mean IOP rise of less than half this value. These results contrast strongly with the present study, in which eyes suffering from COAG treated medically and surgically have similar mean IOP rises of 4.02 mmHg and 5.49 mmHg respectively on changing from the sitting to the lying position. However, it is important to note that Anderson and Grant examined only six eyes which had undergone trabeculectomy, as compared with 159 eyes which were receiving medical therapy, and hence comparisons between the two studies must be limited.

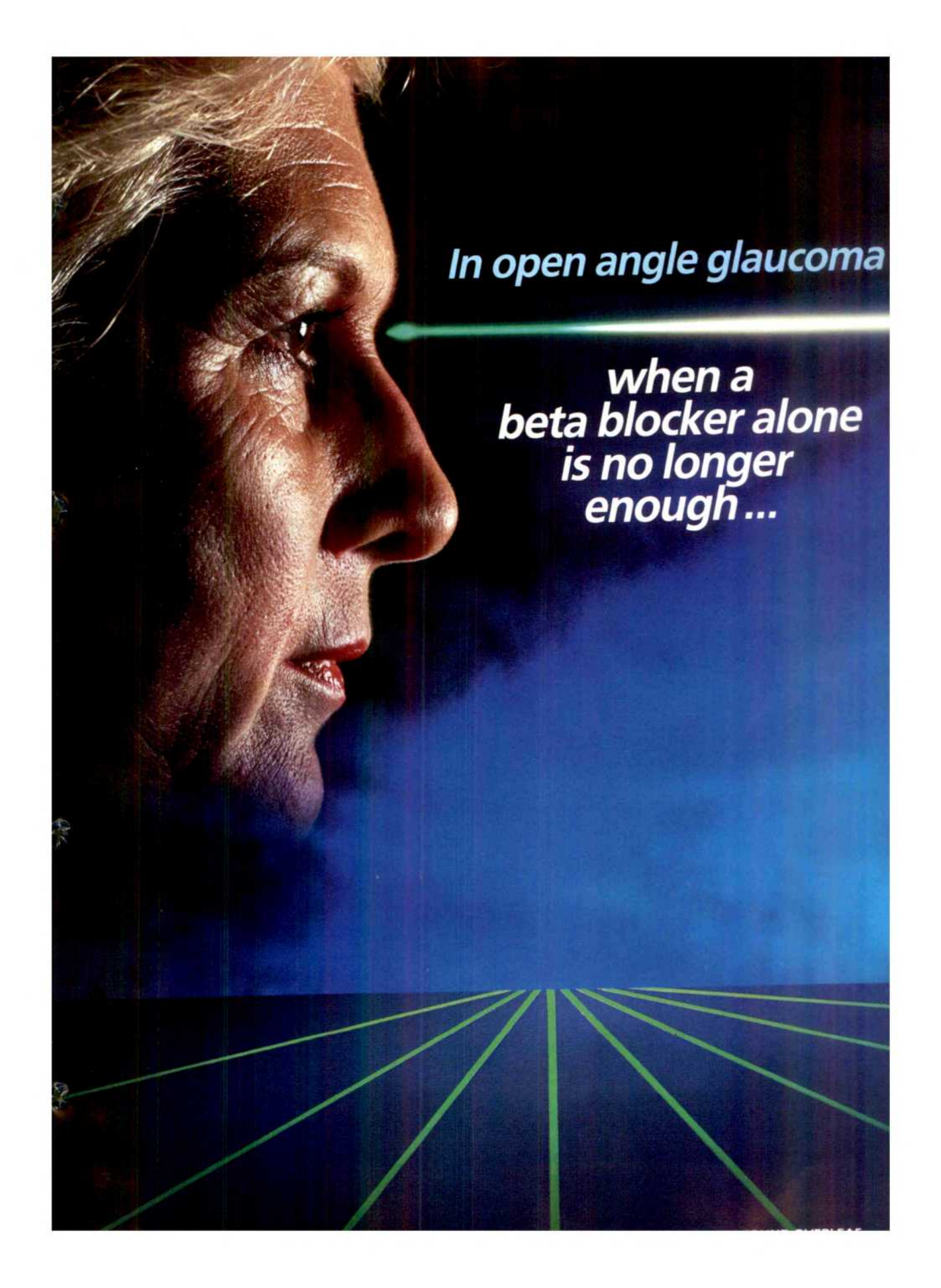
These results confirm the value of IOP measurements in the lying position in patients with COAG,

because the intraocular pressure may be dangerously high on lying down as a consequence of the abnormal postural response. Even in the trabeculectomy groups the mean IOP was above 21 mmHg in the lying position (21.39 and 22.0 mmHg for bilateral and unilateral trabeculectomy respectively). This may account in part for the progression of the disease even when the IOP as recorded by the Goldmann applanation tonometer appears to be within the normal range.

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Efficacy of antiprostaglandin therapy in vernal conjunctivitis

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SUMMARY Twenty-seven patients with vernal conjunctivitis who remained symptomatic following treatment with corticosteroid drops and/or Opticrom drops (sodium cromoglycate 2%, benzalkonium chloride 0.01%) were treated with aspirin. Aspirin produced marked improvement in all patients apart from three. The possible mechanism of the efficacy of aspirin in vernal conjunctivitis is discussed.

Vernal conjunctivitis is a severe perennial form of allergic conjunctivitis involving the conjunctiva and often also the cornea. The condition is found predominantly in children or young adults. The main symptoms are those of severe itching, photophobia, and the production of a tenacious, stringy, mucous discharge. The disease generally affects the upper tarsal conjunctiva with papillary hypertrophy and cobblestone appearance. In severe cases the limbal conjunctiva may also be affected, causing localised oedema and hyperaemia or fleshy isolated vegetations. Punctate keratitis and indolent corneal ulceration may also occur.

The topical application of corticosteroids may be of considerable benefit. But control is not complete in all cases, and its long term use can produce glaucoma. The efficacy of sodium cromoglycate 2% (Opticrom) remains controversial.¹⁻³

Aspirin therapy in mastocytosis was found to be beneficial, and, since the pathophysiology of both mastocytosis and vernal conjunctivitis involves mast cell abnormalities, the use of aspirin in treating the latter was tried in three patients.⁴

We report here the effect of aspirin therapy on 27 patients with vernal conjunctivitis.

Material and methods

Twenty-seven patients aged 4-18 years were treated with aspirin; 24 were males and three were females. All the 27 patients had been treated prior to aspirin

with steroid drops topically and 15 with Opticrom drops too; nevertheless they remained symptomatic. In three patients the disease was so severe that they received prednisone tablets. The patients had been under our follow-up before aspirin treatment for an average of 1.5 years, and the duration of the disease had lasted up to 4 years.

The patients were questioned for photophobia, lacrimation, and itching. On examination they were divided into cases of palpebral, limbal, and mixed type of vernal conjunctivitis, with special emphasis on superficial punctate keratopathy. Twenty-three patients complained of severe photophobia, 22 of itching, and 18 of lacrimation. On examination 14 patients presented with the palpebral type, three with the limbal type, and 10 with mixed vernal conjunctivitis. Twenty patients presented with superficial punctate keratopathy and two had corneal ulcers (nos. 5, 10) prior to aspirin therapy.

The dosage of aspirin in our patients varied between 0.5 g and 1.5 g daily, depending on the patient's age. During aspirin treatment corticosteroid as well as Opticrom drops were withheld. The duration of therapy for the acute inflammatory stage was six weeks, followed by gradual weaning from the drug, clinical findings permitting.

Results

The results are summarised in Table 1. Symptoms improved in 24 patients after treatment with aspirin, though in 20 patients the palpebral hypertrophy remained visible. In four out of 19 patients superficial

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Table 1 Summary of clinical findings prior to and after aspirin treatment

Pat. no.	Sex	Age	Treatment prior to aspirin		Symptoms before aspirin treatment			Signs before aspirin treatment			Symptoms after treatment			Signs after aspirin treatment		
			C-steroids	Opticrom	Photo-phobia	Lacrima-tion	Itch-ing	Palpe-bral type	Super-fic. corneal stippling	Limbal type	Photo-phobia	Lacrima-tion	Itch-ing	Palpe-bral type	Super-fic. corneal stippling	Limbal type
1	M	4	+	+	+	+	+	+	+	-	-	-	±	±	-	-
2	M	8	+	+	+	+	+	+	+	-	-	-	-	+	-	-
3	F	18	+	-	+	+	+	+	+	++	-	-	-	±	-	-
4	M	4	+	+	+	+	+	+	-	++	-	-	-	±	-	-
5	M	5	+	+	+	+	+	+	+	-	-	-	-	+	-	-
6	M	7	+	+	+	+	+	+	+	+	-	-	±	+	-	-
7	M	18	+	+	-	-	+	-	-	-	-	-	-	+	-	+
8	M	7	+	+	+	+	+	+	+	-	-	-	-	±	-	-
9	M	7	+	+	-	+	+	+	+	+	-	-	-	±	-	-
10	M	11	+	-	+	++	+	-	+	++	+	+	-	+	-	+
11	M	6	+	+	-	+	-	+	+	-	-	-	+	+	±	-
12	M	8	+	+	++	+	+	+	-	+	-	-	+	++	+	-
13	M	8	+	-	±	+	+	+	+	-	-	-	-	+	-	-
14	M	8	+	-	+	-	-	+	+	-	-	-	-	+	-	+
15	M	4	+	+	+	+	-	+	+	++	-	-	+	±	-	-
16	M	4	+	-	+	+	+	+	+	+	+	+	+	+	+	-
17	F	6	+	-	+	+	+	+	-	+	-	-	-	+	-	-
18	M	13	+	-	+	+	+	+	-	-	-	-	-	+	-	-
19	M	5	+	-	+	-	+	+	+	+	-	-	-	-	-	-
20	M	11	+	+	+	-	-	+	+	-	-	-	-	-	-	-
21	M	10	+	-	+	-	+	+	+	-	-	-	-	+	-	-
22	M	8	+	-	++	-	-	+	+	-	-	-	-	+	-	-
23	M	6	+	-	+	-	+	+	±	+	-	-	-	+	-	-
24	M	9	+	+	+	+	+	+	-	-	-	-	-	+	-	-
25	M	7	+	+	+	-	+	+	+	-	±	-	-	+	-	-
26	M	6	+	+	+	+	+	-	-	+	-	-	-	-	-	-
27	F	6	+	-	+	-	+	+	+	-	±	-	±	±	+	-

punctate keratopathy remained, and in three other patients limbal papillae were still visible. In this group of patients no adverse reaction to aspirin was observed.

Discussion

The incidence of vernal conjunctivitis is particularly high in Israel, and apparently some of its features are different from those in temperate zones.³ The disease in this country seems to be less seasonal than has been reported elsewhere. It has also been stressed that the incidence of other atopic disorders in children with vernal conjunctivitis was only 11%, which is similar to the incidence of atopic disorders among other children of the same age. This finding may explain why only a selective group of children with vernal conjunctivitis, namely those who present with other allergic conditions, react well to cromoglycate.

In spite of treatment with steroids and cromoglycate our patients remained symptomatic. Mast cell abnormalities characterise both vernal conjunctivitis and mastocytosis, a generalised disease of mast cell proliferation with increased serum levels of hista-

mine and prostaglandin D₂.⁶ Prostaglandin D₂ is the mast cells' most prevalent prostaglandin, and its role in inflammation has been recently appreciated.⁷

In vernal conjunctivitis the percentage of degranulated mast cells is increased, probably signifying prostaglandin release.⁸ The process of degranulation is believed to be due to antigen induced bridging of IgE molecules which are bound to specific receptors on the mast cell surface. Aspirin acts by acetylating the active sites of cyclo-oxygenase, thus interrupting the production of prostaglandin D₂ from its precursor arachidonic acid.⁹ Hence aspirin may block the production of the inflammation producing prostaglandin in mast cells released in vernal conjunctivitis by an antigen-dependent mechanism. Indeed, application of arachidonic acid, the precursor of prostaglandin D₂ produces conjunctival redness and chemosis in rabbits.^{10,11}

We have administered aspirin to 27 patients who, in spite of local steroid drops and/or opticrom, remained symptomatic. After treatment with aspirin the symptoms and signs improved in all but three patients (nos. 12, 16, 27). Aspirin produced marked improvement in the punctate keratopathy and limbal

infiltration in most patients. The cobblestones of the upper tarsus did not disappear but were smaller and less inflamed.

The limitation of this study is that the efficacy of acetylsalicylic acid treatment was not evaluated in a masked fashion. The gravity of the disease in this group, however, prevented us from applying a procedure using a placebo. We believe that the marked improvement in signs and symptoms of vernal conjunctivitis in most patients receiving aspirin only for extended periods of time, following the failure of corticosteroids and cromoglycate, strongly suggests the efficacy of this treatment beyond a placebo effect.

We conclude that aspirin is an additional therapeutic tool in the treatment of vernal conjunctivitis and can be tried as the only treatment in new cases of vernal conjunctivitis, in conjunction with tear drop substitutes to help prevent punctate keratopathy by lubricating the cornea. The clinician must, however, be alert to the possible side effects of aspirin, namely increased bleeding tendency, gastritis, and Reye's syndrome. It may also worsen the bronchial asthma which occasionally occurs in these allergic children.

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Acanthamoeba keratitis

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SUMMARY We report on four patients seen during the past two years who had *acanthamoeba* keratitis. One is described in detail. We believe that *acanthamoebic* eye infection is not rare. An immunofluorescent technique for localisation of amoebae and cysts is described. Our patients' response to propamidine and dibromopropamidine therapy was complicated by problems of toxicity.

Although the first report of the devastating eye infection that can occur with *Acanthamoeba* species was described as long ago as 1974,¹ only scattered publications have appeared since then,²⁻¹⁶ and reports in British journals of cases originating in this country have been few.^{2-5, 15} Several papers have appeared recently in American journals which serve to highlight certain clinical features of the infection and a frequently unsatisfactory outcome, whether medical or surgical treatment or both are given. It is our impression that *acanthamoeba* keratitis is by no means uncommon. We report here that we have seen four patients in the past two years in whom this diagnosis was eventually confirmed. One of them is considered in detail, with a description of an immunofluorescent technique for localisation of amoebae and cysts.

Case report

A 31-year-old man was first referred in November 1984 for further management of a refractory left herpes simplex stromal keratitis. At that time he had a visual acuity of 6/24 in this eye and an extensive stromal opacity with a 1.5 mm central indolent ulcer. He was on prednisolone 1% eyedrops four times a day. He had also had a dendritic ulcer in the right eye some years earlier, which had healed uneventfully, with no visual deficit or further problems to date.

He had first presented with a dendritic ulcer in the left eye in August 1984; and this had healed with antiviral therapy, but a disciform keratitis ensued. In October 1984 he was noted to have a ring infiltrate. At this stage, while on a visit to the United States, he developed a fresh corneal abscess and hypopyon. Although cultures were negative, a presumptive

diagnosis of bacterial keratitis was made, and his eye settled on topical systemic antibiotics.

His eye gradually deteriorated during December 1984, and his visual acuity fell to 6/60. He was noted to have a variable indolent epithelial defect. Treatment at this stage consisted of prednisolone eyedrops 0.3-1%, acyclovir eye ointment five times a day, gentamicin (Genticin) eyedrops four times a day and atropine eyedrops twice a day. By January 1985 he had developed stromal thinning beneath the central indolent ulcer and a bandage contact lens was fitted. Two months later the central infiltrate had extended but a clear periphery was maintained. The cornea had epithelialised by May 1985 while use of the bandage lens continued, though the eye remained inflamed, and visual acuity was hand movements. In summary, therefore, this man had had a nine-month history of a chronic stromal keratitis following a dendritic ulcer, with an indolent ulcer which was perhaps compatible with herpes simplex keratitis but was remarkably recalcitrant.

It had been impossible to quieten the eye with steroids, as is usually the case in patients with herpetic stromal keratitis. As he was experiencing very protracted pain and disability an 8 mm therapeutic penetrating keratoplasty was carried out in June 1985. At surgery it was found that the aqueous was markedly viscous, which accords with a case described by Hirst *et al.*¹¹ The corneal disc was sent for histological and microbiological examination. Within 36 hours of culture on *Escherichia coli* seeded nutrient free agar, *acanthamoeba* trophozoites were identified on the plate. Subsequent periodic acid Schiff (PAS) staining of the corneal sections revealed multiple *acanthamoeba* cysts in the stroma (Fig. 1). These cysts were also identified by an immunofluorescent technique as follows.

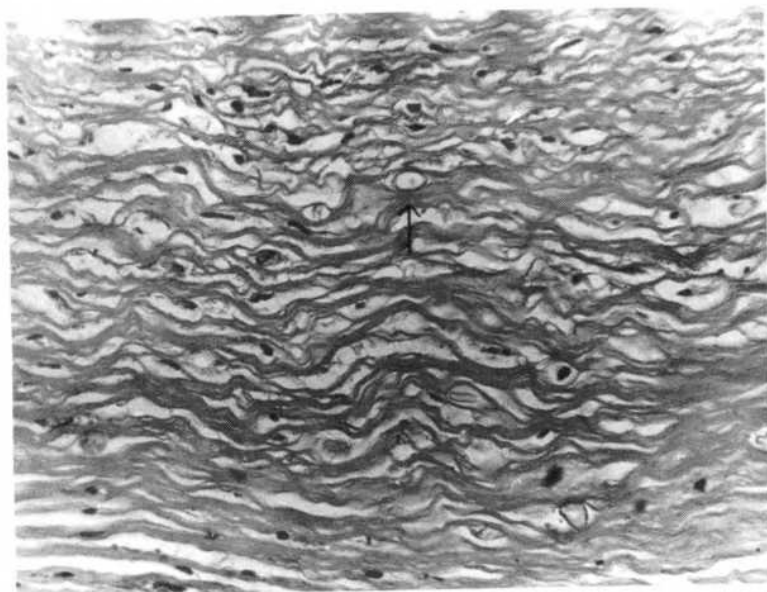


Fig. 1 *Acanthamoeba* cysts in corneal disc. Periodic acid Schiff stain.

IMMUNOFLUORESCENT LOCALISATION OF AMOEBAE AND CYSTS

Wax-embedded sections of the corneal disc were dewaxed and brought to 50% ethanol. After they had been dried and rinsed with waterproof marker, a 1/50 dilution of rabbit anti-*Acanthamoeba* serum¹⁷ in phosphate buffered saline (PBS) was layered on the sections. They were held at room temperature for 30 minutes in a moist box. After two 10-minute washes in PBS, fluorescein-conjugated sheep antirabbit Ig serum was added at a dilution of 1/50 and further held for 30 minutes. Two further washes in PBS were followed by a five-minute exposure to 1/10 000 Evans blue and a final five-minute PBS wash. After being mounted under a cover slip in pH 7.1 glycerol mountant (Difco), the sections were examined under a Neofluor $\times 25$ objective with incident blue light in a Zeiss fluorescent microscope. Cysts and amoebic trophozoites fluoresced yellow-green.

TREATMENT

Postoperatively he was treated with chloramphenicol eyedrops qds, dexamethasone eyedrops qds, acyclovir eye ointment qds, cyclopentolate eyedrops bd, Brolene eyedrops qds, and Brolene eye ointment nocte. Brolene is the trade name for a preparation containing propamidine and dibromopropamidine which is widely available in chemists without prescription. He did well initially, maintaining a clear corneal graft for several months. In September 1985 some loose suture loops occurred which were removed. His treatment at this time was prednisolone eyedrops qds, acyclovir eye ointment

tds, Brolene eyedrops qds, and Brolene eye ointment nocte. In October 1985 he was noted to have epithelial thickening and irregularity over the graft and it was felt that these changes were due to Brolene toxicity. Brolene therapy was therefore reduced and stopped over a 10-day period. However, when seen the following week he was noted to have an epithelial defect, an active anterior chamber, keratic precipitates over graft and host, and a small hypopyon. This was thought to represent a recurrence of *acanthamoeba* in the graft. Brolene therapy was restarted at two-hourly intervals. Within a few days his eye had quietened down considerably, and the epithelial defect had regressed. Since then he has had further epithelial defects. His visual acuity has varied between 6/18 and 6/60 postoperatively, and this limitation is mainly due to a posterior subcapsular cataract. Current therapy is prednisolone eyedrops qds and Brolene eyedrops qds.

Discussion

Acanthamoebae are free-living amoebae found in the soil, water, and air. The trophozoites are uninucleate, have small spiky acanthopodia, and move slowly on a broad front.¹⁸ There is a resistant cystic stage characterised by angular double-walled cysts. In outdoor air it has been found that an average of one amoebic cyst of any species was found in 9.1 m³ of air and one cyst of *Acanthamoeba castellanii* in 18.2 m³.¹⁹ Since 1974 this ubiquitous organism has been implicated as the causative agent in some cases of chronic stromal keratitis. Two groups of patients

seem to be particularly at risk of developing acanthamoeba keratitis. The first are individuals who have otherwise normal, immunocompetent eyes who receive some form of ocular insult as from trauma or the wearing of a contact lens that brings the organism directly to the compromised ocular surface. Secondly, there are those who are already under treatment for herpetic and possibly other stromal keratitis; they may have been on topical steroids for prolonged periods which allow the opportunistic acanthamoeba infection to occur.

In the past two years our department has been involved in the diagnosis of four patients with acanthamoeba keratitis; this suggests that it is not a rare condition. Three of these patients first had chronic herpetic keratitis, whereas the fourth appears to have developed acanthamoeba keratitis as a result of ocular trauma from a tennis ball that had been lying in a manured rose bed.

In most of the cases reported so far the diagnosis was made following a therapeutic keratoplasty, and three were made as a result of enucleation. However, the recent report of a cure for the condition by medical means¹⁵ indicated that early diagnosis may now lead to prospects of an early cure, with avoidance of the morbidity and pain that are such frequent features of the condition and a better prognosis than has been obtained hitherto. It is our view that the diagnosis should be earnestly sought early on in all patients with refractory stromal keratitis. Attempts should be made to identify acanthamoeba by corneal scrapings, microscopy, and culture. Acanthamoeba infections seem particularly likely if there has been soft contact lens wear,¹⁴ herpes simplex keratitis, contact with dirty water, a variable epithelial defect, uveitis, hypopyon, a ring infiltrate,¹⁶ corneal thinning, descemetocoele formation, or excessive ocular pain.

Somewhat surprisingly, a retrospective histological review of 756 cases of penetrating keratoplasty corneal sections collected between 1960 and 1975 revealed no cases of acanthamoeba infection.²⁰ However, another recent retrospective analysis of 300 specimens collected between 1974 and 1983 revealed definite evidence of acanthamoeba infection in two.¹⁵ Although these figures suggest that the condition is rare, the increasing number of reports testifies otherwise. This may be because of increased awareness and diagnosis or because of a real increase in incidence related to greater use of soft contact lenses and more liberal use of topical corticosteroids.

Wright *et al.* recently reported the first medical cure of acanthamoeba keratitis using a combination of Brolene and neomycin.¹⁵ It is interesting that our patient remained well while on Brolene therapy until signs of toxicity developed; when he stopped these

drugs, there was probably a recurrence of the acanthamoeba keratitis. This presumed flare-up, which was not proved by culture, settled rapidly on restarting Brolene therapy. His recurrent epithelial defects may represent further problems of toxicity, perhaps compounded by neomycin or partially treated recurrent disease. Thus, while Brolene offers prospects for an early cure, there are still unanswered questions as to the appropriate frequency and duration of treatment. These answers may be forthcoming with increased awareness and diagnosis of acanthamoeba ocular disease.

We are indebted to colleagues from Moorfields Eye Hospital (R J Cooling), Truro (C K Jones), Northampton (A J Atkinson), and Charing Cross Hospital (P Kinnear), who referred these patients. Mrs Julie Lawrence typed the manuscript.

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Stickler's syndrome: a study of 12 families

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SUMMARY Stickler's syndrome is a congenital disease of connective tissue with considerable ocular and non-ocular lesions. This study reports 12 pedigrees (10 families and two isolated cases) and evaluates some peculiar ocular aspects not previously reported in the syndrome.

According to recent reports^{1,2} the term Stickler's syndrome indicates a hereditary disease of connective tissue together with ocular lesions (such as vitreoretinal degeneration and retinal detachment with giant tears), orthopaedic and otolaryngological lesions, a peculiar facial physiognomy, and a characteristic body habitus. During the last year I have studied 12 pedigrees (10 families and two isolated cases), a total of 39 individuals in all, affected by Stickler's syndrome. All 12 probands had retinal detachment. A diagnosis of Stickler's syndrome was made on the basis of ocular lesions (mainly retinal detachment in high congenital myopia, vitreoretinal degeneration) and non-ocular lesions. Subsequently the family history of the probands was studied to identify affected relatives.

The purpose of my study was to evaluate mainly (1) the association between the ocular and non-ocular pictures in Stickler's syndrome, (2) the variability of expressivity among the different pedigrees and even in the same family among the different generations, and (3) the possibility of a classification into different groups. In addition the study presents some peculiar aspects of the ocular pictures in the patients examined such as ectopia lentis and star shaped or semilunar cataracts, that are probably associated with the general disorders of connective tissue. To my knowledge these aspects have not been reported previously in the description of Stickler's syndrome.

Material and methods

Of the 39 people examined 20 were males and 19 females. Their ages ranged from 4 to 60; however, only two cases were over 40. A medical history was taken from the 39 patients. The ophthalmic examination placed particular emphasis on high congenital myopia, congenital cataract, ectopia lentis, study of

the angle, examination of the vitreous and the retina by slit-lamp and Goldmann three-mirror lens, observation by binocular indirect ophthalmoscope, fluorescein angiography and sometimes electroretinography, and A and B scan ultrasonography. The non-ocular examination including observation of the characteristic physiognomy, consisting of an Asiatic appearance, flattened nose, long philtrum, small upper lip, receding chin, cleft palate, abnormal teeth, hyperextensibility of the large joints, and a characteristic habitus. X-rays of various parts of the body and audiograms were made of all 12 probands and of some of the other patients.

Results

OCULAR EXAMINATION Myopia. 87% of the patients were myopic. In the probands the myopia was always over 10D sph and increased with age, contrary to what has been previously reported.¹ Lacquer cracks or neovascular membranes were not found in any of the myopic patients.

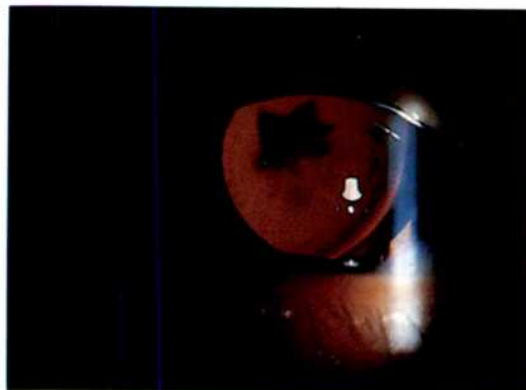


Fig. 1 Star shaped cataract with ectopia lentis.



Fig. 2 Congenital cortical cataract with semilunar aspect.

Lens. 49% of the patients had presenile cataract. Some of these were subcapsular cataracts, while others were cortical opacities with peculiar features (star shaped or semilunar) (Figs. 1,2).

Ectopia lentis. This was present in five cases (12.8%); in two it was bilateral and congenital (Fig. 3). In these two last cases the lenses were dislocated upwards and temporally, while in the remaining three cases the lenses were dislocated into the vitreous. Owing to the youth of the patients it was difficult to evaluate the possibility of previous trauma. It was possible to exclude other ocular and systemic disorders that generally cause ectopia lentis.⁴

Intraocular pressure. Ocular hypertension was present in 10% of the patients. Few cases had glaucomatous field loss.

Angle aspect. In 26% of the patients long and

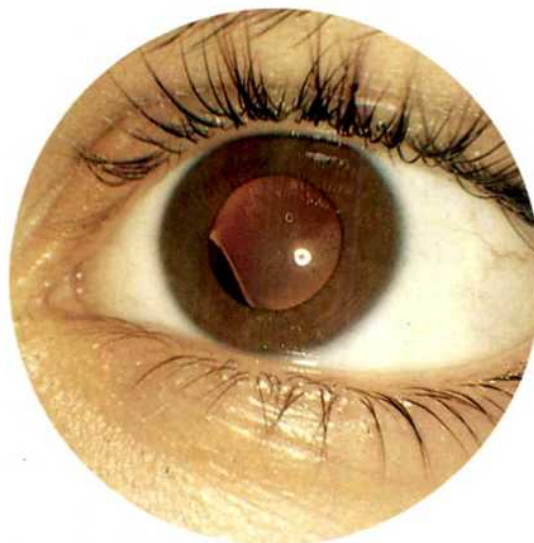


Fig. 3 Ectopia lentis.



Fig. 4 Large syneresis with pocket and circumferential equatorial adhesions.

thick iris processes stretched to the trabecular meshwork and covered part of the ciliary face and scleral spur in the anterior chamber angles. This picture is very similar to that seen in the Marfan syndrome,^{5,6} Marfan-like syndrome,⁷ Stickler's syndrome,⁸ and sometimes pathological myopia.

Vitreous. 85% of the patients and all probands had vitreous abnormalities. The vitreous often appeared to be optically empty on slit-lamp examination. A syneresis with fenestrated vitreous membranes and circumferential equatorial adhesions was present in other patients (Fig. 4).

Fundus. There were alterations in both posterior and peripheral retina in 87% of the patients. Notwithstanding the high degree of myopia, a myopic crescent was not often seen. This may have been due to the fact that some of the patients were very young. It has been noted that congenital myopia may increase with age, and so some characteristic degenerations, such as myopic crescent, may develop later. Sometimes an irregular and deformed appearance of the optic disc was seen, associated with straightening of retinal vessels at the posterior pole. Most patients were found to have hypopigmentation of the fundus (fundus flavus). Some patients showed a typical radial perivascular chorioretinal degeneration (Fig. 5).

But the most characteristic appearances were in the peripheral retina and, in particular, in the temporal periphery. These areas were studied by fluorescein angiography and ophthalmoscopy. In many cases it was possible to observe interruption of

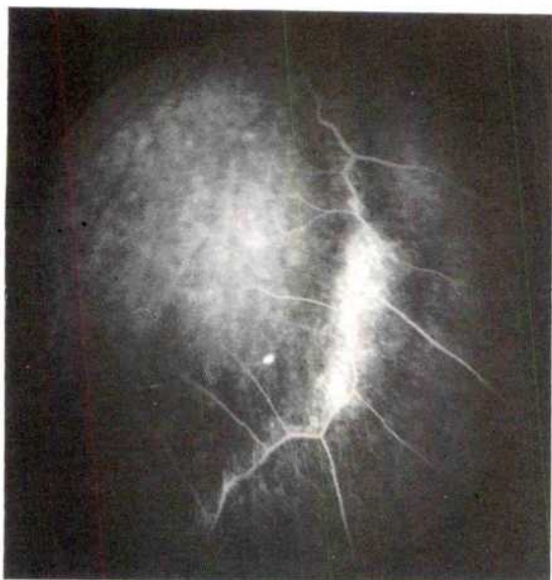


Fig. 5 Radial perivascular chorioretinal degeneration.

the retinal vessels in equatorial areas and sometimes further posteriorly (Figs. 6a and 6b). In some cases the retinal vessels became sheathed and showed signs of leakage (Fig. 7). Hard exudates were present where the leakage was profuse. In other cases non-perfusion was observed, with a notable alteration in the configuration of the retinal vessels (Fig. 8). Although the same type of vascular changes seen in our patients may occur in dominant exudative vitreoretinopathy (DEV),^{9,10} in no case did we detect the dense, radially orientated capillaries that are characteristic of DEV. Twenty-one of the 39 patients (55%) had retinal detachment and six cases had giant retinal tears greater than 180°. A female child with a Pierre-Robin anomaly had a 360° giant retinal tear. In all these cases the other eye showed vascular and retinal abnormalities. Electroretinography gave normal results in 12 cases examined.

NON-OCULAR EXAMINATION *Orthopaedic results.* Abnormalities of the joints were present in many patients, including laxity and hyperextensibility (23%), width of joints (21%), articular click (44%), and morning stiffness (21%). The patients with hyperextensibility of the joints did not have excessively wide joints, while, on the contrary, patients with reduced flexibility had notably wider joints. 21% of the patients had a Marfanoid habitus, while 13% had a Weill-Marchesani habitus. The last two types of habitus were also present in two members of the same family.

X-ray results. These have been previously

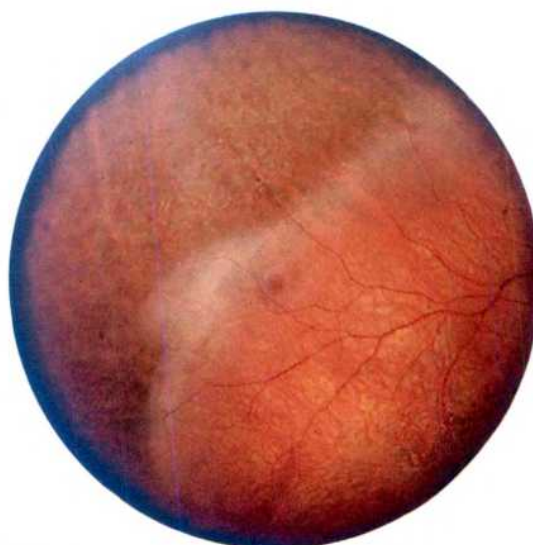


Fig. 6a

Figs. 6a, 6b Temporal quadrant of the fundus: note the interruption of the retinal vessels and no development of the retinal tissue.

described in detail.^{2,3,11} The roentgenographic studies showed evidence of generalised epiphyseal dysplasias which may affect any of the joints. All 12 propositi and some other patients showed this type of lesion.

Facial appearance. Many of the patients had a peculiar physiognomy characterised by a flattened bridge of the nose (41%), maxillary hypoplasia

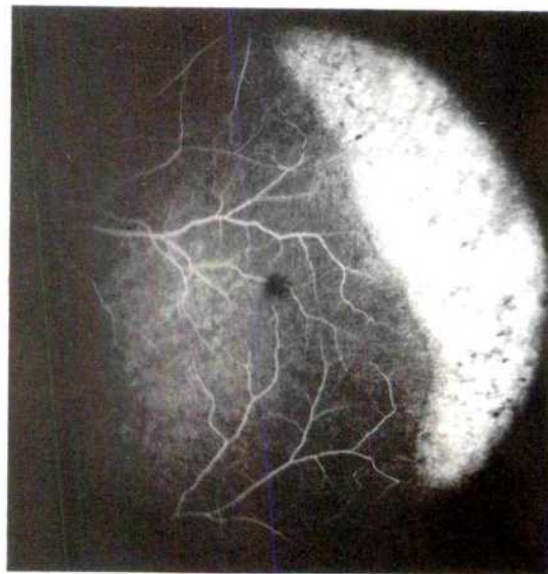


Fig. 6b

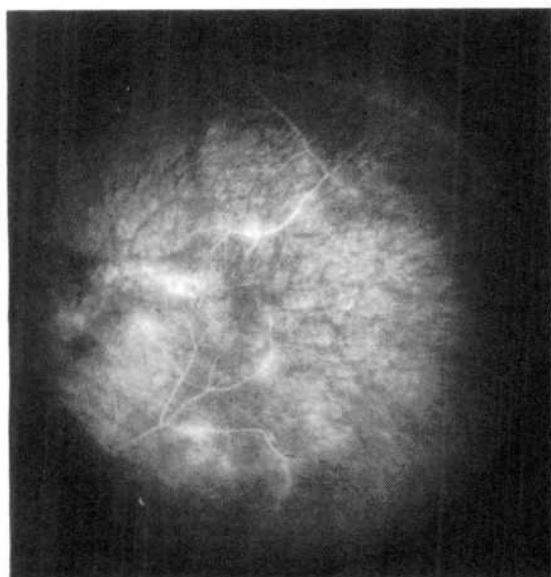


Fig. 7 Mild leakage of the retinal vessels near the posterior pole.

(31%), epicanthus (15%), receding chin (18%), small upper lip (23%), long philtrum (13%), and trycomegalia (13%).

Otolaryngology signs. Cleft palate was present in 18% of the patients, while 31% had a highly arched or submucous palate. Two of these patients had been diagnosed at birth as having Pierre-Robin syndrome. About 46% had malocclusion and 21% hearing loss.

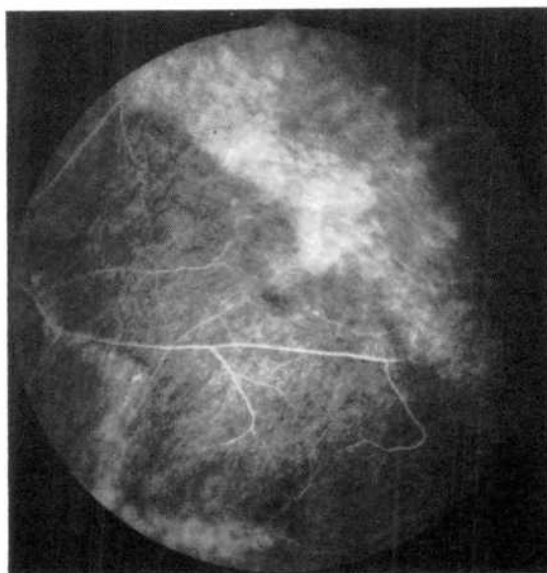


Fig. 8 Arrest of the peripheral vascularisation with alterations in the configuration of the retinal vessels.

These last percentages are lower than those reported by other workers,¹ probably owing to the youth of my patients.

Genetic results. Two of my patients were sporadic cases and therefore probably new mutations. In the remaining 10 pedigrees an autosomal dominant inheritance was always clearly demonstrated.

Discussion

Before the classic description of Wagner in 1938 of a large Swiss family with hereditary hyaloideoretinal degeneration¹² some authors had reported retinal detachment in some pedigrees. For example, Lang in 1885 reported retinal detachment in two brothers.¹³ In 1930 Bane also reported retinal detachment in a family.¹⁴ These two last works do not describe the vitreous degeneration, and the pedigree of Wagner does not present retinal detachment. In 1966 Jansen reported on two Dutch families and 44 cases which showed hereditary hyaloideoretinal degeneration; in them retinal detachment was quite frequent.¹⁵ One year before Stickler *et al.*¹⁶ had described for the first time the association between vitreoretinal problems and premature degenerative changes in various joints under the name 'hereditary arthro-ophthalmopathy.' Subsequent descriptions^{3,8,11,17} reported large pedigrees in which a characteristic physiognomy, cleft palate, and orthopaedic lesions were associated with vitreoretinal degeneration and retinal detachment. Knobloch¹¹ radiologically examined families affected by Wagner's syndrome and discovered that 20 of the 21 patients suffered from arthropathies of varying degrees. These reports have shown that in Stickler's syndrome a pathological hereditary association between ocular and non-ocular disorders may exist and that the lesions are extremely variable in their expressivity. Maumenee¹⁸ has classified these syndromes into six distinct groups and considers that probably two or more gene loci are involved in them.

My studies show that in Italy Stickler's syndrome is rather common. It is important to make an early diagnosis so that prompt treatment of the ocular and non-ocular disorders and genetic counselling may be given. Furthermore, in agreement with other authors⁸ I believe that Stickler's syndrome is a single entity. In fact none of the families examined in this study fitted exactly into any of the recognised categories proposed by Maumenee. For example, when the first 10 patients of one of our families were visited in our department, they were initially diagnosed as having Wagner's syndrome. We then examined two other members of this family who suffered from typical joint changes described in Stickler's syndrome. In another family the father, who is completely blind from bilateral retinal detachment, might be classified

as having a Weill-Marchesani-like syndrome (according to Maumenee). By contrast in the same family the two children, 14 and 13 years old, with serious retinal problems, show a Marfanoid habitus. Moreover, in the remaining pedigrees the clinical pictures are not always unequivocal, and various signs of connective tissue diseases frequently overlap. From the genetic point of view I think that probably only a single gene is involved. It has an autosomal dominant inheritance with a large range of expressivity and large pleiotrophic effects. The phenotypic consequences probably differ owing to the correlation between this hypothetical gene and the genetic background.

There are many ways in which disorders of connective tissue may affect the ocular system. The main ocular disorders seen in my studies of Stickler's syndrome are (1) high congenital myopia, (2) vitreoretinal and chorioretinal degeneration, and (3) retinal detachment. As other authors¹⁵ have found, I believe that high myopia in my patients is always congenital. In fact most of the myopic patients were very young. I had frequently observed some peculiar features of pathological myopia such as 'fundus flavus' and retinal vessels of an irregular configuration. This finding is important because pathological myopia might always be considered a heredo-degenerative entity, which is entirely different from ocular elongation and is often associated with other heredo-degenerative conditions.^{19,20} In the patients examined, detachment of the retina was the most disabling consequence of this syndrome. It is worth noting that the ophthalmoscopic and fluorangiographic aspects of the fellow eye in all patients with monolateral retinal detachment were very unusual – in particular in the temporal mid-periphery, where it was possible to see the interruption of the retinal vascularisation near the equator with atrophic changes of the retina. Knowledge of these changes is important for early prophylaxis of the retinal detachment.

Hagler *et al.*²¹ reported a group of 33 patients with an unusual but specific type of retinal degeneration characterised by pigment clumping round retinal vessels, with underlying atrophy of the pigment epithelium. This degeneration was frequently associated with malignant forms of retinal detachment. In the majority of patients in Hagler's series a family pattern was present. This author thought the degeneration probably represented a distinct clinical entity different from that described by Wagner. On the contrary, I saw this type of retinal malformation in many of my patients who showed clear signs of Stickler's syndrome. I believe that these alterations are due to disturbances in the complex correlation between the developing retinal vascular system and

the vitreous. This interference leads to inhibitions in the normal development of the retinal vessels and therefore to malformations of the inner retinal layers. Apart from high myopia, retinal detachment, and vitreous degeneration, other ocular aspects such as ectopia lentis, which have never been described before in Stickler's syndrome, were found in my patients. As others have noted^{19,20} some of my patients also showed angle abnormalities, as frequently seen in the Marfan syndrome and sometimes in pathological myopia. In my study this aspect was not associated with a Marfanoid habitus or with ectopia lentis. This result confirms the overlapping between the different signs of the Stickler's syndrome.

My studies have shown that Stickler's syndrome is frequent and often incorrectly diagnosed. It is therefore extremely important to continue to study the biochemical processes of connective tissue disorders in this syndrome.

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Effects of the encircling procedure on the aqueous flow rate in retinal detachment eyes: a fluorometric study

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SUMMARY Fluorophotometry was carried out in nine cases of unilateral non-traumatic rhegmatogenous retinal detachment successfully treated by a combination of local buckling and an encircling procedure with a silicone band. After topical instillation of fluorescein the change in its concentration in the anterior chamber was followed, from which the loss rate of the dye from the anterior chamber (k_0) and the cornea-aqueous transfer coefficient ($k_{c,ca}$) were estimated. The thickness of the cornea and the anterior chamber volume were also measured, and the aqueous flow rate and the corneal endothelial permeability were calculated in individual eyes. The examinations performed 4-18 months after operation showed that the aqueous flow rate in the operated eye fell to 85 (SD 12)% of that in the fellow control eye ($p < 0.005$). In the operated eye the anterior chamber volume also fell significantly, and the corneal endothelial permeability may have decreased. Ocular hypotension after the detachment surgery with encirclement was attributable to a decrease in the aqueous flow rate.

It is well documented that rhegmatogenous retinal detachment is usually associated with low intraocular pressure (IOP),¹ for which two mechanisms have been suggested: (1) reduced formation of the aqueous humour^{2,3} and (2) fluid outflow through the retinal break and choroid.^{4,5} But it has also been reported that the IOP in an eye with rhegmatogenous retinal detachment remained lower than in the healthy fellow eye after the retina was reattached successfully.^{9,10} The encircling procedure produced more pronounced and long-standing postoperative ocular hypotension.^{9,10} Furthermore, Friedman and Neumann reported that in 11 out of 12 eyes with primary open-angle glaucoma after the rhegmatogenous retinal detachment was successfully operated the IOP decreased for 1 to 5.5 years without any antiglaucoma treatment, while it was still necessary to control the IOP in all 12 fellow eyes.¹¹ Similar findings have been reported by several authors, and they are compatible with the above observation.¹²⁻¹⁴

The mechanism of the low IOP in the successfully treated eye with retinal detachment has not been fully studied yet. To the best of our knowledge only a

study using tonography has been reported, which suggested it should be attributed to reduced aqueous humour formation.¹¹ However, as the ocular rigidity was altered after the retinal detachment surgery, especially after operations with an encircling procedure,^{9,10,15,16} the apparent aqueous flow rate estimated from the apparent facility of outflow, without a correction for the effect of ocular rigidity, would need cautious interpretation. In the present report, the aqueous humour dynamics in successfully treated cases of unilateral, non-traumatic, rhegmatogenous retinal detachment were studied by fluorometry, which is now believed to give the truest information on the aqueous flow rate in the living eye.^{17,18}

Materials and methods

SUBJECTS

Nine patients with unilateral, non-traumatic, rhegmatogenous retinal detachment aged 21 to 65 years were included in this study (Table 1). They were operated upon in the University of Tokyo Branch Hospital from February to December 1982 by one of the authors (KM) with a combination of equator parallel scleral buckling using a silicone strip

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Table 1 Data of subjects

Subject	Age	Sex	Extent of detachment (quadrant)	Area of exoplant (degree)	Period* (month)
1	53	M	3	90°+encircling	4
2	49	F	2	150°+encircling	6
3	40	M	4	180°+encircling	5
4	45	M	1	90°+encircling	8
5	55	M	1	60°+encircling	7
6	65	F	4	90°+encircling	7
7	64	F	2	120°+encircling	7
8	21	F	4	90°+encircling	18
9	61	M	2	90°+encircling	7

* Period between surgery and fluorometry.

exoplant (No.31s or 32s) and an encircling procedure using a silicone band (No.240s) (Medical Instrument Research Associates Inc., Waltham, Mass); tightening of the encircling band was adjusted to give an indentation of about 1 mm. All retinal breaks were sealed by cryopexy or postoperative photo-coagulation, and no diathermy was used. In all cases the retina was successfully reattached at the first operation, and no significant complications during the operation or during postoperative follow-up were encountered. The fundus examination of the fellow eyes revealed peripheral retinal degenerations but no retinal tears or holes. The patients had no ocular and systemic disorders other than retinal detachment.

FLUOROMETRY

The fluorometric examination was carried out four to 18 months (eight months on an average) after the surgery. Before the fluorometric measurement was carried out informed written consent was obtained from each subject. At 9 am a 15 μ l of 30% sterile solution of sodium fluorescein was gently instilled on to the cornea of both eyes. The subjects were asked to blink several times and then to keep their eyes closed for about one minute. Five minutes after the instillation the conjunctival cul-de-sac was washed thoroughly with physiological saline. The fluorescence intensities in the central part of the cornea and the anterior chamber were then measured every hour for seven hours with a slit-lamp fluorometer (Tokyo Optical Co. Ltd., Tokyo, Japan) and the fluorescein concentrations in the anterior chamber were determined by correcting the influence of the fluorescence in the cornea on that in the anterior chamber as previously described.¹⁹ At two hours after the instillation the thickness of the cornea (CT) was measured with a Haag-Streit pachymeter modified by Mishima,²⁰ and at four hours the anterior chamber was photographed according to the method of Johnson *et al.*²¹ The anterior chamber depth was read from the photograph by means of a standardised

anterior chamber scale and the volume of the anterior chamber was calculated.²¹ At the end of the fluorometric measurements the anterior segment of the eye was examined in detail by slit-lamp microscope, and the IOP was measured with a Goldmann applanation tonometer. All measurements and examinations were carried out by one of the authors (MA) without knowing the laterality of the previous history of retinal detachment.

METHOD OF DATA ANALYSIS

As the method of calculating the aqueous flow rate from the change in concentration of fluorescein in the anterior chamber was described in detail previously,¹⁹ only a brief outline will be given.

According to the two-compartment model of Jones and Maurice,¹⁷ the concentration change in the anterior chamber after a single dose to the cornea can be written as follows:^{17,22}

$$C_a = (M_0/V_a) (k_{c,ca}/(B-A)) (\exp(-At) - \exp(-Bt)) \quad (1)$$

where A is equal to $\{(k_{a,ac} + k_{c,ca} + k_o) -$

$$\sqrt{(k_{a,ac} + k_{c,ca} + k_o)^2 - 4k_{c,ca}k_o}\}/2,$$

and B is equal to $\{(k_{a,ac} + k_{c,ca} + k_o) +$

$$\sqrt{(k_{a,ac} + k_{c,ca} + k_o)^2 - 4k_{c,ca}k_o}\}/2,$$

and $k_{a,ac}$ is equal to $(V_{c,ca}/V_a) k_{c,ca}$.²² The symbols used here are: C_a , the mean concentration in the anterior chamber; M_0 , the amount in the cornea at time 0; $k_{a,ac}$, the aqueous-cornea transfer coefficient in reference to the anterior chamber volume; $k_{c,ca}$, the cornea-aqueous transfer coefficient in reference to the corneal volume; k_o , the loss rate from the anterior chamber; V_c , the volume of the cornea; V_a , the volume of the anterior chamber; r_{ca} , the cornea-aqueous distribution ratio.²² The values of $k_{c,ca}$ and k_o were estimated from the obtained data series of the fluorescein concentration in the anterior chamber, C_a , by means of Marquardt's method of least squares fitting applied to equation 1 using a M-280H computer (Hitachi Electric Co., Tokyo).^{19,23}

Table 2 Results of measurements

Subject	IOP (mmHg)		Anterior chamber depth (mm)		$V_a(\mu\text{l})$		CT (mm)	
	Op	F	Op	F	Op	F	Op	F
1	13	15	3.0	3.4	174	242	0.52	0.52
2	18	17	3.3	3.8	185	218	0.51	0.50
3	10	8	3.2	3.5	208	243	0.51	0.51
4	8	14	2.8	3.0	177	183	0.52	0.53
5	14	16	3.1	3.4	203	206	0.52	0.52
6	16	12	2.5	2.7	136	153	0.52	0.51
7	10	12	1.9	2.0	82	86	0.52	0.52
8	10	14	2.5	2.7	150	176	0.52	0.52
9	9	16	2.8	3.0	144	161	0.51	0.51
Mean	12	14	2.6	3.1	162	185	0.52	0.51
S.D	3	3	0.9	0.5	39	50	0.01	0.01

Op = operated eye. F = fellow control eye. For explanation of V_a and CT see text.

In carrying out the calculation the measured volume of the anterior chamber was used as V_a . V_c was assumed to be $70 \mu\text{l}$,²⁴ and r_{ca} was assumed to be 1.7 .²⁰

Results

The results of the measurements are summarised in Table 2 and the results of the calculations in Table 3. The aqueous flow rate was calculated by $k_o \times V_a$,¹⁷ and the corneal endothelial permeability coefficient (P_{ac}) was calculated by $k_{c,ca} \times r_{ca} \times 0.9 \times CT$.²⁰

No significant difference was seen between both eyes in the IOP and CT (paired t test, $p > 0.1$). On the other hand the aqueous flow rate ($p < 0.005$), V_a and the depth of the anterior chamber ($p < 0.01$) were significantly lower in the operated eyes. The ratio of operated eye to fellow eye averaged 0.85 (SD 0.12) for the aqueous flow rate and 0.91 (SD 0.10) for P_{ac} ($n=9$). When these ratios were compared with the

left-right ratios for the aqueous flow rate and the P_{ac} obtained in normal Japanese – 0.99 (SD 0.05) for each ($n=11$)¹⁹ – the ratio of operated eye to fellow eye for aqueous flow rate was significantly lower than the left-right ratio obtained in normal persons (unpaired t test, $p < 0.005$), but that for P_{ac} was not significantly different from the left-right ratio obtained in normal persons ($p > 0.05$). The anterior segment of the eye appeared to be normal on slit-lamp microscopic examination.

Discussion

METHOD

The present method of calculation needs the value of r_{ca} , which was assumed to be 1.7 according to the result obtained after systemic administration of fluorescein.²⁰ However, recent studies showed that systemically administered fluorescein is rapidly metabolised to fluorescein glucuronide, and most of

Table 3 Results of calculations

Subject	K_o (hour ⁻¹)		Aqueous flow rate ($\mu\text{l}/\text{min}$)		$k_{c,ca}$ (hour ⁻¹)		P_{ac} ($\times 10^{-4} \text{cm}/\text{min}$)	
	Op	F	Op	F	Op	F	Op	F
1	0.38	0.46	1.10	1.86	0.23	0.30	3.0	4.0
2	0.64	0.69	1.97	2.51	0.38	0.44	4.9	5.6
3	0.63	0.60	2.18	2.43	0.40	0.40	5.5	5.2
4	0.53	0.59	1.56	1.80	0.32	0.35	4.2	4.6
5	0.71	0.84	2.40	2.80	0.44	0.52	5.8	6.9
6	0.73	0.83	1.65	2.04	0.39	0.43	5.0	5.6
7	0.71	0.66	0.97	0.95	0.30	0.28	4.0	3.7
8	0.74	0.73	1.85	2.14	0.41	0.43	5.4	5.7
9	0.57	0.54	1.37	1.45	0.31	0.31	4.0	4.0
Mean	0.63	0.66	1.67	2.00	0.35	0.38	4.6	5.0
S.D	0.12	0.13	0.49	0.57	0.07	0.08	0.9	1.0

Op = operated eye. F = fellow control eye. For explanation of k_o , $k_{c,ca}$, and P_{ac} see text.

the fluorophore in the plasma or in the anterior chamber after systemic administration of the dye is not fluorescein itself but fluorescein glucuronide.^{25,27} This compound is also fluorescent, though more weakly than fluorescein is.^{25,26} Thus it is possible that the value of r_{ca} determined after systemic fluorescein mainly reflected that of fluorescein glucuronide rather than fluorescein. Indeed in the rabbit cornea the value of r_{ca} determined after exclusion of the influence of fluorescein glucuronide was twice as great as that determined after systemic fluorescein.²⁸ As the estimates for k_o and $k_{c,ca}$ calculated by the present method were influenced by variation in the r_{ca} value,¹⁹ it is probable that the estimates obtained here are somewhat different from the 'true' value of k_o and $k_{c,ca}$ for fluorescein. The value of r_{ca} , which is thought to reflect binding of the dye to the stromal tissue²⁹ should have no significant individual variations in the normal cornea, and the values for fellow eyes showed no significant difference.²⁰ Thus the influence of a variation in r_{ca} values on the calculation must be very similar in both eyes of an individual, and it is justifiable to compare the values of k_o and $k_{c,ca}$ determined by the present method in both eyes to examine the difference between the 'true' k_o and $k_{c,ca}$.

The value of k_o is expressed by the sum of the values of the transfer coefficient by flow (k_{fa}) and by diffusion ($k_{d,pa}$).^{17,22} As k_{fa} accounts for more than 90% of k_o ,^{17,23} the aqueous flow rate, $k_{fa} \times V_a$, was approximated by $k_o \times V_a$ in the present study. A decrease in the k_o found in the operated eye may be interpreted as being due to a decrease in the $k_{d,pa}$ rather than a decrease in the k_{fa} . However, it seems quite unlikely that the value of $k_{d,pa}$, an index of the blood-aqueous barrier permeability, was lower in the operated eye than in the fellow unoperated eye, though no fluorometric measurements after systemic fluorescein were carried out in the present study. An increase in the blood-aqueous barrier permeability, if any, would give a rise in the value of k_o , but not in reduction.

AQUEOUS FLOW RATE

The aqueous flow rate in the operated eye was decreased to 85% of that in the fellow eye and the reduction in the aqueous flow rate was thought to be responsible for the well documented postoperative ocular hypotension after retinal detachment surgery with an encircling procedure.^{9,10} The method used to measure the aqueous flow rate in this study estimates the rate of the aqueous humour movement through the anterior chamber, but does not estimate the rate of the aqueous humour formation into the posterior chamber. The lower aqueous flow rate observed in the present subjects may be explained by either one

or both of the following two mechanisms: (1) reduction in the net aqueous humour formation or (2) increase in posteriorly directed outflow of the aqueous humour.

It is well documented that the scleral buckling procedures, especially that with encirclement, are followed by shallowing of the anterior chamber in the early postoperative period.^{29,31} This shallowing is probably attributable to the change in the ciliary body and zonule due to the compromised blood drainage from the ciliary body caused by the scleral buckle.^{31,33} The blood leaving the ciliary body is mainly drained into the vortex veins, and, in the monkey eye, if three or four vortex veins are injured, the ciliary body became markedly congested.³³ In the rabbit eye an encircling procedure reduced the ciliary blood flow, probably owing to compromised venous drainage.³⁴ A postoperative change in the flow characteristics of the blood was reported in the eye which underwent an encircling procedure.¹⁰ Under these conditions it seems likely that the function of the ciliary epithelium is also affected, resulting in the reduction of the aqueous humour formation. In the present subjects the anterior chamber depth was 16% shallower in the operated eye than in the fellow eye. This fact suggests that the ciliary body in the operated eye of the present subjects was still not in a normal physiological condition, having not fully recovered from the postoperative changes. This favours the explanation that the reduced aqueous humour formation was mainly responsible for the reduced aqueous flow rate observed.

On the other hand there is increasing evidence that, in the eye with rhegmatogenous retinal detachment, a fluid flow exists from the posterior chamber through the vitreous cavity and retinal breaks and across the retinal pigment epithelium.^{7,35-37} But at the present stage of investigation no information is available on the question whether it still exists after the retina is reattached surgically. The intact retina is a barrier to the movement of water across it.³⁸ The retina undergoes structural changes when it is detached, but it restores normal morphology and also probably its resistance against the movement of water, after the detachment is surgically repositioned.^{39,40} The retinal break on the other hand is thought to remain as a defect in the retina even after surgical reattachment.

Furthermore, the diffusion of peroxidase was greater across the photocoagulated scarred retina than across the normal retina.⁴¹ Thus it is possible that the fluid outflow from the posterior chamber through the scarred retinal break and choroid exists also after the retina is reattached. If this is the case, the postoperative decrease in the aqueous flow through the anterior chamber and the resultant

ocular hypotension are likely to be of long duration, because a window in the barrier against water movement would remain almost as permanently as the scarred retinal breaks, and the encirclement itself should have little influence on the postoperative IOP.

However, it is known that ocular hypotension after retinal detachment surgery gradually decreases and that encirclement produces more pronounced and long-standing postoperative IOP change.^{9,10} These facts suggest that this postoperative IOP change is associated with some non-physiological changes in the eye caused by surgery which gradually disappear postoperatively. Since the postoperative change in the anterior chamber depth also improves gradually,^{29,31} it seems likely that the postoperative ocular hypotension is related to the postoperative congestion and swelling of the ciliary body, and resultant reduced formation of aqueous humour, rather than the fluid outflow through the scarred retina.

CORNEAL ENDOTHELIAL PERMEABILITY

The corneal endothelial permeability coefficient, P_{ac} , to fluorescein is a quantitative index of the barrier function of the corneal endothelium.²⁰ The value of P_{ac} appeared to be lower in the operated eye than in the fellow eye of the present subjects. However, no significant difference was seen between the ratio of operated eye to fellow eye and the left-right ratio found in normal persons. Consequently it is difficult to draw a conclusion on the P_{ac} difference observed here, because of the variability of P_{ac} measured by this technique used at present and also the variability of P_{ac} between the right and left eyes of normal persons. The value of P_{ac} in the normal persons as measured by this method¹⁹ was significantly smaller than the values obtained both in the operated and the fellow eyes of the present subjects (unpaired *t* test, $p < 0.05$). It has been reported that the fellow eye in cases of unilateral rhegmatogenous retinal detachment had a decreased IOP and abnormal tonographic findings, suggesting some underlying pathology in these eyes.^{5,42,43} Although the difference in the P_{ac} found here was not highly significant, it may suggest that the corneal endothelium is functionally not completely normal in patients with non-traumatic rhegmatogenous retinal detachment.

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Adenocarcinoma of retinal pigment epithelium

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SUMMARY This report describes a 41-year-old man with an intraocular tumour misinterpreted clinically as choroidal melanoma. The fluorescein angiographic features were not fully characteristic of uveal malignancy, and indeed histopathology revealed the diagnosis of adenocarcinoma of the retinal pigment epithelium. It is suggested that, in cases with the fundus and angiographic findings described here, the rare possibility of adenocarcinoma of retinal pigment epithelium should be kept in mind. Of particular interest were the changing pathological findings in the various parts of the tumour, which paralleled the fluorescein angiographic pattern.

Adenocarcinoma of the retinal pigment epithelium is a very rare neoplasm which is notoriously difficult to diagnose clinically and has always prompted enucleation because of its resemblance to choroidal melanoma.¹⁻⁵

This report describes the case of a male patient who underwent enucleation for a retinal mass that looked like a melanoma and seemed to grow during a follow-up period of one year. The angiographic characteristics were not fully suggestive of melanoma, and indeed the histopathological studies revealed the tumour to be an adenocarcinoma of the retinal pigment epithelium. In such a rare condition, where reports on individual patients constitute the main source of knowledge of the tumour characteristics, it seems worthwhile to publish our case, both for what it illustrates and for the areas of ignorance it exposes.

Case report

A 41-year-old male was admitted for investigation following the diagnosis of an intraocular tumour in his left eye. The initial symptoms had appeared six months before admission, when he complained of metamorphopsia and disturbances of visual acuity in his left eye.

Ocular examination revealed an entirely normal right eye with 20/20 visual acuity. In his left eye the vision was 20/40, the intraocular pressure was normal, and no anterior segment abnormalities were present,

except for a few cells in the anterior part of the vitreous.

Ophthalmoscopic examination disclosed in the upper temporal quadrant of the left fundus a well defined pigmented mass, abruptly protruding into the vitreous (Fig. 1). The lesion occupied an area of about 5 disc diameters and was more pigmented in its nasal side. Some subretinal glial reaction was seen in its inferonasal border, which was continued by a serous detachment extending towards the macula. The retinal vessels adjacent to the tumour were dilated and tortuous along the whole of their length. No orange discolorations or drusen were disclosed on the surface of the tumour.

On fluorescein angiography the tumour failed to show uniform fluorescence (Fig. 2). In its nasal part no fluorescence was disclosed throughout the entire angiographic study. The temporal part of the tumour on the other hand showed early hyperfluorescence, which gradually increased in intensity. The two afferent arteries – one dilated and the other of normal calibre – filled rapidly and seemed to penetrate the tumorous mass (Fig. 2). The tortuous efferent vein was rapidly filled by fluorescein, indicating increased volume of flow through a possible arteriovenous shunt. The sensory retinal elevation appeared in the lower part of the tumour (Fig. 3). The retinal gliosis adjacent to the nasal border of the tumour showed late staining (Fig. 4).

Laboratory and general medical evaluation failed to provide any pertinent findings that could have been related to the ocular lesion.

During the following year the tumour increased slightly in size. As the general consensus of opinion

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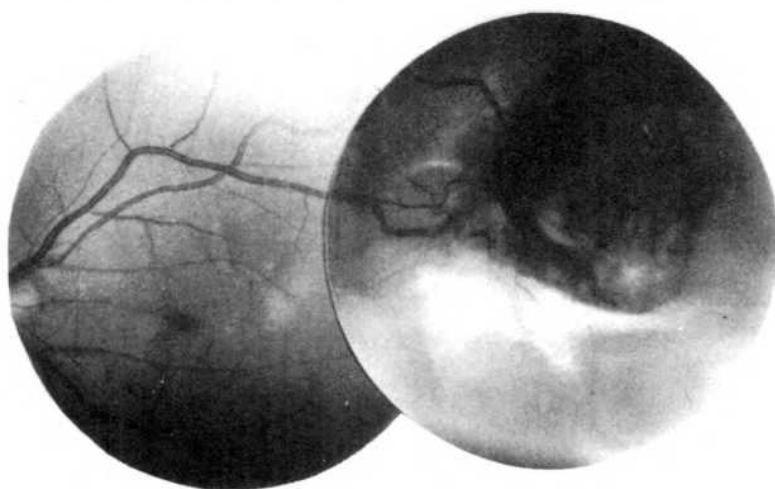


Fig. 1 The tumour located temporally to the macular region, jet black in its nasal part and discoloured on the temporal side (red-free).

was that the lesion could be a choroidal melanoma, surgery was recommended. The patient underwent an uncomplicated enucleation, and no extraocular extension was noted at the time of operation.

PATHOLOGICAL FINDINGS

The specimen consisted of an intact left eye. The globe transmitted light readily except for a round area of about 6 mm in diameter on the temporal side. The globe was sectioned, and a well demarcated, heavily pigmented tumour appeared in the supero-temporal quadrant.

A marked variation in the histological structure of the nasal and temporal side of the tumour was observed (Fig. 5). In the nasal part the pigmentary content of the tumour as a whole was higher, the cells were more densely arranged, and they were separated by less stromal tissue. On the temporal side the tumour contained areas of low cell density with more abundant stroma. The penetrating afferent artery could also be visualised in the histological preparation (Fig. 5).

The tumour mass was composed of cuboid or columnar pigmented epithelial cells typically

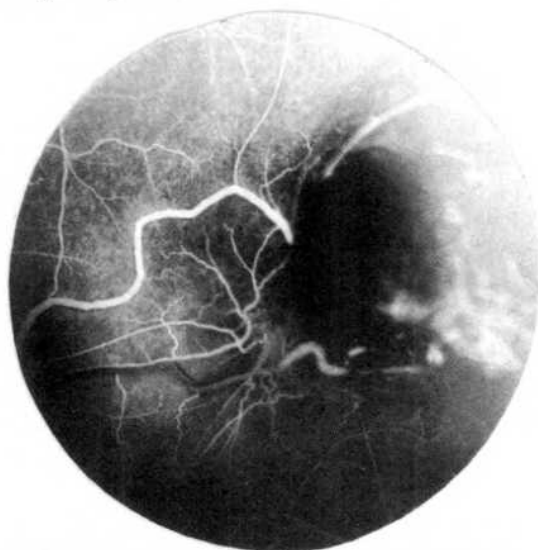


Fig. 2 On the arterial phase of the angiogram the tumour remains hypofluorescent in the nasal part, and one of the afferent arteries which seems to penetrate the mass is dilated. The efferent vein is tortuous and fills precociously.

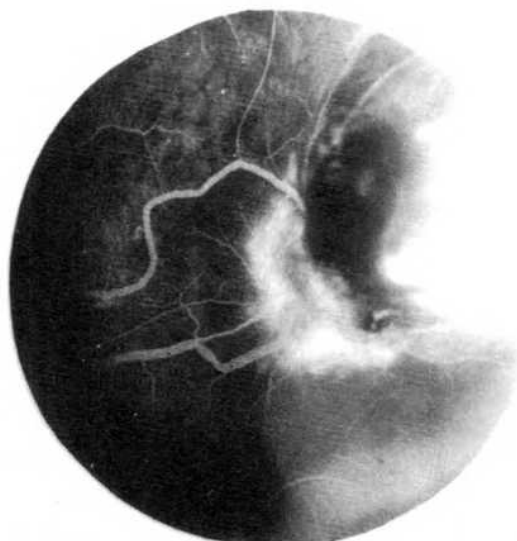


Fig. 3 Arteriovenous phase of the angiogram with sensory retinal elevation on its inferior part.

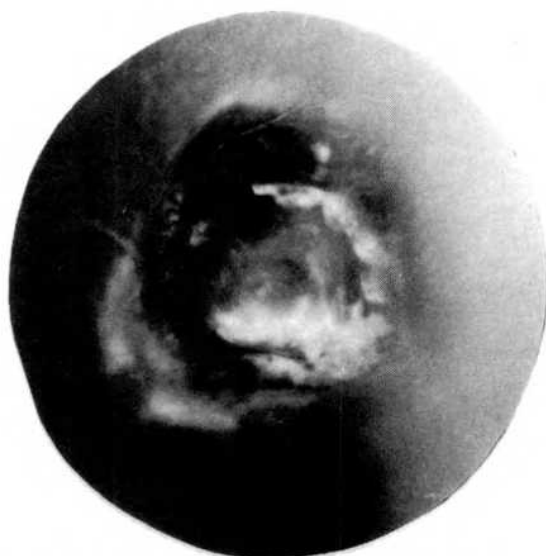


Fig. 4 Late non-homogeneous staining of the tumour.

arranged in pseudoglandular pattern (Fig. 6). They were attached to membrane-like structures. In routine haematoxylin-eosin preparations the cells were so deeply pigmented that cytological details were not discernible. In bleached histological sections the tumour cells appeared as clusters of epithelial cells varying in shape and having an adenoid disposition (Fig. 7). Mitotic figures were rarely seen, and the occasional cells in mitosis had sparsely pigmented granules. The cytonuclear anomalies were characterised mainly by giant nuclei with prominent nucleoli (Fig. 8).

Along the surface of the choroid, round the border of the tumour, recognisable retinal pigment

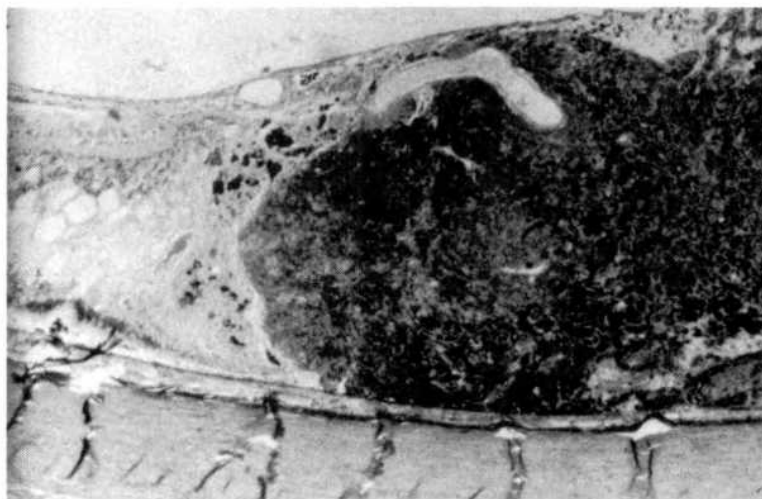
epithelium appeared to change its structure from normal to abnormal morphology. The Bruch's membrane was intact on all the sections examined (Fig. 5). At the nasal border of the mass the adjacent retina underwent gliosis. In some parts of the preparation tumour cells directly invaded the retinal layers, which were totally destroyed over the dome of the lesion.

Discussion

Adenocarcinoma of the retinal pigment epithelium is an infrequently encountered tumour which may masquerade as choroidal melanoma. Its rarity and the usual failure to diagnose it clinically has precluded successful recognition before enucleation and histopathological examination. A review of the literature confirms that clinical and angiographic descriptions of histologically proved adenocarcinoma of the retinal pigment epithelium have been few, and its appearance in a male subject seems to be exceedingly rare.^{1,3,4}

The histological examination in our case was crucial, and its results were characteristic enough to make the correct diagnosis. The tissues in the vicinity of the tumour and its continuation with normal retinal pigment epithelium led us to believe that the mass represented a neoplasm of pigment epithelial origin. The intact Bruch's membrane also supported the pigment epithelial origin of the tumour without the issue being clouded by simultaneous choroidal involvement. Its invasive nature to the adjacent layers and its pseudoglandular configuration pointed to the diagnosis of adenocarcinoma. The tumour did not appear to be malignant cytologically, nor did it develop any metastases during a seven year follow-up.

Fig. 5 General histological aspect of the tumour, retinal vessel penetrating the mass. Note the regional differences in pigmentation of the tumour tissue and the intact Bruch's membrane.



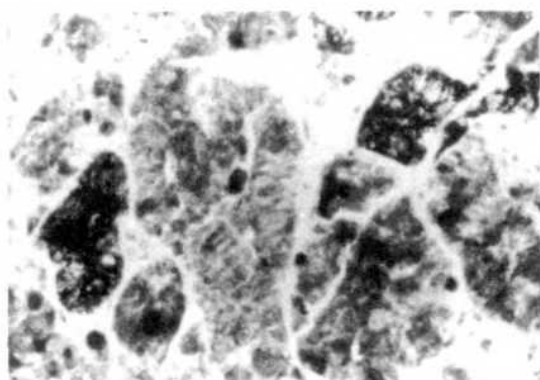


Fig. 6 Pseudoglandular disposition of the tumour cells.

The opportunity of demonstrating the angiographic pattern of this case and its correlation with the tumour's structural characteristics were unique. Fluorescein angiography revealed some of the gross anatomical features of the tumour, and it was of assistance in detecting and defining some of the structural alterations in the tumour tissue. The nasal side of the mass showed no evidence of fluorescence either early or late in the study, and the tumour in this region appeared darker than on its temporal side. The presence and significance of these regional differences in fluorescein patterns was clarified by histological study, which correlated well with the angiographic results (Table 1). The inability to detect fluorescence on the nasal side of the tumour was thought to be due to the dense pigmentation acting as a barrier and so preventing the exciter light source from activating the fluorescein. However, on the temporal side, where the pigment was sparser and the amount of extracellular space larger, fluorescein

Table 1 Ophthalmoscopic and histological correlations

<i>Biomicroscopy</i>	<i>Angiography</i>	<i>Histopathology</i>
Nasal third of the tumour jet black	Early and late hypofluorescence (blocked hypofluorescence)	Very dense pigmented cells with pseudoglandular pattern in a reduced stromal area
Temporal part of the tumour showing discoloration	Early and late hyperfluorescence (window defect and late staining)	Sparsely pigmented cells in a more abundant stroma
Glial proliferation	Late staining	Retinal gliosis
Serous retinal detachment	Sensory retinal elevation	Cystoid retinal oedema
Afferent artery and efferent vein	Early and rapid filling, high volume of flow	Artery found in the tumour; presumed arteriovenous shunt

readily diffused into the more abundant tumour stroma.

Some additional aspects of the ophthalmoscopic features which may shed light on the clinical diagnosis of this condition merit specific attention. The intensely black colour of the tumour, its abruptly ascending borders, the dilatation of the adjacent retinal vessels, and the lack of surface orange discolorations could suggest that this case did not present a typical choroidal melanoma. Angiography indicated an increased intravascular volume, and the changes in the haemodynamics were thought to be produced via an arteriovenous shunt. Retrospectively it seems that awareness of all these characteristics and their correct interpretation could have obviated the mistaken diagnosis. Although the specificity of such features is not sufficiently high

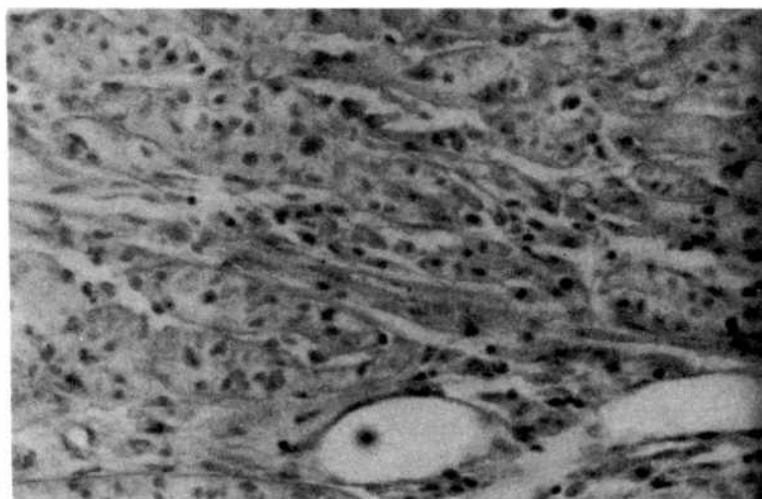


Fig. 7 Bleached section with adenoid disposition of the tumour cells.

Fig. 8 Bleached preparation showing the giant nuclei with prominent nucleoli (arrow).



to allow complete dependence on them, it seems prudent to observe patients with enlarged afferent and efferent vessels leading to a pigmented retinal tumour over a longer time.

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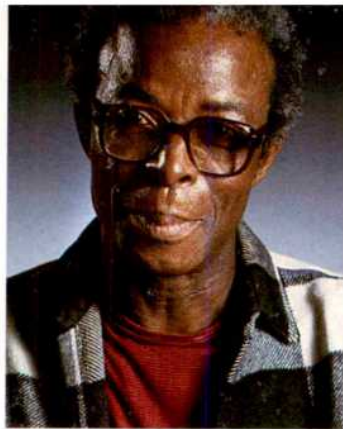
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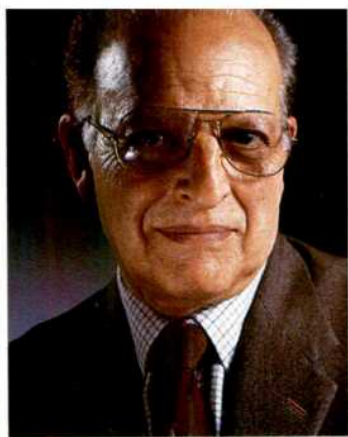


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Diplopia after retinal detachment surgery

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SUMMARY Diplopia following retinal detachment usually responds to simple measures. Fifteen out of 311 cases developed diplopia lasting more than three months after conventional retinal detachment surgery. Binocular single vision was restored in 12 of the 15 cases (80%). The mean follow-up was four years. Diplopia was eliminated stepwise. If prisms were ineffective, our first surgical procedure was removal of the scleral buckle. If the retina was flat, we were prepared to remove the buckle early. When diplopia persisted after buckle removal, we proceeded to strabismus surgery. Our most consistent results followed strabismus surgery on the untreated eye. Prisms alone restored binocular single vision in six patients (40%), one of whom preferred to adopt a compensatory head posture. Removal of the scleral buckle restored binocular single vision in three patients (20%), with the help of a prism in one case and a compensatory head posture in another. Binocular single vision was restored after buckle removal and strabismus surgery in three further patients (20%), one requiring a prism in addition. Binocular single vision was not restored in three patients (20%).

Diplopia occurs in 3% to 30% of patients after conventional retinal detachment surgery.¹⁻⁵ Possible causes include the breakdown of an existing fusion weakness, distortion of the globe by scleral buckles, damage to the rectus muscle insertions by traction sutures, and postoperative tissue swelling.⁶⁻¹¹ Permanent adhesions and scarring often bind the rectus muscles down to the underlying sclera.¹⁰⁻¹³ Most cases of diplopia following retinal detachment surgery recover spontaneously. Rectus muscles swollen by cryotherapy return to normal after six weeks.⁸ Even when division of the rectus muscles was more widely practised, and diathermy was used instead of cryotherapy, heterotropia was usually transient.^{10-11,14,15} It has been postulated that phoria adaptation contributes to the resolution of the initial heterotropia after retinal detachment surgery.¹⁶ Phoria adaptation is observed when the normal fusional range is restored after any induced shift of oculomotor balance.

Many of those with transient diplopia learn to suppress the image from the operated eye, particularly if its acuity is reduced. It has been estimated that between one-quarter and one-third of all patients develop suppression in the treated eye after retinal detachment surgery.^{5,9,17} There are some who cannot suppress the second image; the ability to

suppress lessens with age, and intractable diplopia may even occur after surgery on amblyopic eyes.¹⁸ Diplopia resolves spontaneously in most cases after retinal detachment surgery, but sometimes persists to become incapacitating. We have studied a group of 15 patients whose diplopia persisted longer than three months after retinal detachment surgery.

Material and methods

Four hundred and thirty-six consecutive cases requiring retinal detachment surgery at St Thomas's Hospital from 1 January 1979 to 31 December 1982 were studied. Surgical techniques included cryotherapy and full-thickness scleral buckling with either Silastic sponges of standard sizes, or solid Silastic bands, gutters, and tyres. 3/0 silk sutures under the rectus muscles provided traction on the globe, but the muscle insertions were not divided. Closed pars plana vitrectomy was performed in 125 of the cases studied.

An orthoptic assessment was performed as soon as any patient complained of double vision after retinal detachment surgery. This orthoptic examination included the measurement of visual acuity and the range of ocular movements. Serial Hess charts were recorded, and the prism cover test was used to measure the angle of heterotropia (the modified

Krimsky test was substituted when the visual acuity was poor). Binocular functions were assessed with Bagolini's striated glasses, the Titmus stereotest, and the synoptophore. Further orthoptic and ophthalmic examinations were conducted at three and six monthly intervals.

First we tried to control diplopia with either adhesive Fresnel prisms or with a prismatic addition to the existing spectacles. We operated only if prisms failed to control the diplopia. Our initial surgical procedure was removal of the scleral buckle, and adjacent rectus muscle insertions were freed of scar tissue at the same time. We performed strabismus surgery as a separate procedure in two cases and combined it with buckle removal in one case.

Results

No patient complained of diplopia after vitrectomy (125 cases). Of 311 patients undergoing conventional retinal detachment surgery 15 (4.8%) developed postoperative diplopia lasting more than three months. Clinical details of these patients are summarised in Table 1, and the effect of scleral buckling

in each case is shown in Table 2. The period of follow-up ranged from two to six years, mean four years.

TIME OF ONSET

Diplopia occurred after the first scleral buckling procedure in 11 of the 15 cases (73%). Double vision was usually present within a few days of retinal surgery, but in three cases its onset was delayed: case 7 had complete unilateral ptosis, case 11 noticed diplopia only after the correction of aphakia, and case 4 was an unreliable witness.

RESPONSE TO PRISMS

At first, fusion was restored with prisms in 11 cases (73%). Seven of these 11 patients still need prisms (47%) but four no longer use them. Two developed a compensatory head posture (cases 6 and 9); and two required strabismus surgery after an initial success with prisms (cases 13 and 15). Five of the seven patients still using prisms needed no other treatment (cases 1-5). Fusion with prisms was achieved by the two remaining patients, after removal of the scleral buckle in case 8, and after removal of buckle and strabismus surgery in case 14.

Table 1 Clinical course of patients with diplopia after retinal detachment surgery

Case no	Age	Number of retinal operations	Maximum heterotropia after retinal surgery (prism dioptres)	Time of buckle removal (months after retinal surgery)	Maximum heterotropia after buckle removal (prism dioptres)	Strabismus surgery	Present status	Corrected visual acuity of operated eye after retinal detachment surgery
1	75	1	R/L 6 Exo 16	—	—	No	BSV (prisms)	6/9
2	60	1	R/L 2 Exo 8	—	—	No	BSV (prisms)	6/9
3	58	2	R/L 6 Exo 6	—	—	No	BSV (prisms)	6/60
4	57	1	Eso 8	—	—	No	BSV (prisms)	6/12
5	61	1	R/L 9 Exo 14	—	—	No	BSV (prisms)	6/6
6	63	1	L/R 13 Exo 18	—	—	No	BSV (with CHP)	6/36
7	54	1	R/L 14 Exo 8	18	L/R 2 Exo 8	No	BSV	6/9
8	68	1	R/L 16 Exo 14	15	R/L 4 Exo 8	No	BSV (prisms)	6/9
9	31	1	R/L 3 Exo 10	10	R/L 1 Exo 6	No	BSV (with CHP)	6/6
10	54	2	L/R 9 Exo 12	—	—	No	Torsional diplopia	6/36
11	21	1	R/L 2	—	—	No	Weak fusion with intermittent diplopia	6/9
12	27	3	L/R >20 Exo 8	5	L/R 14 Exo 6	No	Suppresses	6/60
13	34	2	L/R 2 Eso 20	5	L/R 2 Eso 25	Yes	BSV	6/6
14	62	1	R/L 20 Exo 18	14	R/L 3 Exo 16	Yes	BSV (prisms)	6/9
15	46	1	R/L 20 Exo 16	3	R/L 20 Exo 16	Yes	BSV	6/18

R = right eye; L = left eye; Exo = exotropia; Eso = esotropia; BSV = binocular single vision; CHP = compensatory head posture.

Table 2 Details of episcleral buckling and its effects in patients with diplopia after retinal detachment surgery

Type of buckle	Case No.	Diameter of sponge(s) (mm)	Muscle(s) in contact with scleral buckle	Maximally restricted ocular movement	Number of patients with diplopia
Silastic sponge explant:	radial	1	5	LR	Adduction
		7	5/7-5	SR	Elevation
	circumferential	8	4	SR/LR	Depression
		2	5	SR/LR	Depression
		14	5	SR	Elevation
		15	5	IR/LR	Elevation/ adduction
	oblique	9	5	IR	Elevation
		12	7-5	IR	Elevation
		6	7-5	—	Depression
		4	—	—	Abduction
Encirclement alone	4	—	—	—	1
Encirclement + gutter	11	—	SR	Elevation	1
Encirclement + sponges	5	5/5	—	Elevation	
	13	5/7-5	—	Abduction	
	3	7-5/7-5	—	Depression	
	10	7-5/7-5	—	Elevation/ adduction	4
Total cases			9		15

LR = lateral rectus muscle. SR = superior rectus muscle. IR = inferior rectus muscle.

Prisms were of no benefit in four cases (27%). Case 10 had torsional diplopia which was relieved by occlusion. Case 11 had very weak fusion with intermittent suppression, case 12 suppressed completely, and case 7, with a large vertical tropia, was able to fuse after removal of the scleral buckle.

RESPONSE TO CORRECTIVE SURGERY

Removal of the scleral buckle. The scleral buckle was removed in seven cases (47%) between three and 18 months after retinal detachment surgery. Changes in the position of the eyes are recorded as changes in the prism cover test readings in Table 1. Diplopia was eliminated completely in only one patient (case 7), who had a large hypotropia. There was a reduction of the heterotropia in three patients: one became orthophoric with prisms (case 8), one controlled the diplopia with a compensatory head posture (case 9), and the other suppressed (case 12). No change was seen in case 15, but the diplopia was actually worse after buckle removal in the two remaining patients (case 13 and 14); their clinical course is described below.

Strabismus surgery. Three patients (cases 13, 14, and 15) required definitive surgical correction of their strabismus. Case 13 had a medial rectus recession and lateral rectus resection on the buckled eye, but even with prisms horizontal diplopia was not controlled. Medial rectus recession and lateral rectus resection in the fellow eye eventually resolved the esotropia without the need for prisms. In case 14 the scleral buckle was removed at the same time as resection of the superior rectus muscle. Vertical diplopia persisted because of overcorrection, and further

surgery was necessary. The superior rectus muscle was recessed and residual diplopia was eliminated with prisms. Case 15 had an exotropia, with hypotropia in the buckled eye. After removal of the scleral buckle strabismus surgery was performed only on the fellow eye: the lateral rectus was recessed and the medial rectus was resected, with downward transposition of the muscle insertions. Although there was some reduction of the hypotropia, diplopia was not controlled, and further strabismus surgery was needed. Recession of the inferior oblique was combined with further surgery to the horizontal recti, an adjustable suturing technique being used. Diplopia was eliminated in all directions of gaze except extreme laevodepression.

Discussion

Several factors influencing the occurrence of diplopia after retinal detachment surgery have been proposed. They include operative trauma, repeated retinal surgery, and the size, location, and type of scleral buckle used.

The importance of minimising operative trauma by careful surgical technique has been stressed repeatedly.^{6 10 11 19-24} A rectus muscle was divided at the time of retinal surgery in only one of our patients (case 12). The inferior rectus muscle had been detached from its insertion twice before, and its tendon was never identified on exploration of the residual scar tissue. In all other cases the rectus muscle insertions were located, and their integrity was guaranteed by passing traction sutures beneath them. It has been suggested that repeated retinal

detachment surgery is a significant cause of postoperative diplopia,⁶ but we did not confirm this finding: 11 of our patients (73%) developed diplopia after their first retinal operation (Table 1).

Prospective studies have indicated that the size of a buckling element, and its location under a rectus muscle, may influence the onset of postoperative diplopia.^{5,6,23,25} Wide-diameter buckles (7.5 mm or wider combinations) were used in eight (53%) of our cases (Table 2). We found that circumferential sponges were associated with diplopia in six cases (40%) and radial or oblique sponges in three cases (20%), which is in contrast to the conclusion of a recent study.⁵ Only one of our 15 cases was treated with an encircling band alone (case 4), a procedure which is less often associated with diplopia,⁹ though cases have been reported with varying frequency.^{16,23,26,27} This factor probably accounts for the absence of diplopia in the 125 vitrectomy cases in our series. Nine of our 15 patients with diplopia (60%) had a scleral buckle directly related to one or more rectus muscles (Table 2). Restricted ocular rotation in the direction away from the rectus muscle with the underlying scleral buckle occurred in six of these cases.^{5,12,19,27,28} In the other three patients (cases 7, 11, 14) elevation was limited, and the scleral buckle lay beneath the superior rectus muscle, causing a mechanical restriction. A vertically acting muscle (superior or inferior rectus) was involved in eight of these nine cases. This finding is strikingly similar to a report of cases in which the rectus muscle adjacent to the scleral buckles were all detached at the time of retinal surgery.¹⁹

Eleven patients (73%) have confirmed the benefit of prisms in the course of their treatment.^{5,15,17,28,29} Five patients (33%) had their symptoms controlled by the use of prisms alone. It is worth emphasising that seven patients (47%) still require prisms to maintain binocular single vision (Table 1). Torsional diplopia cannot be controlled by prisms, although surgical correction is possible. However, in case 10, we resorted to occlusion and did not attempt strabismus surgery.³⁰

It has been stated that no surgical correction of postoperative diplopia should be attempted until six months have elapsed after retinal detachment surgery.^{15,20} However, our experience of buckle removal suggests that its timing is not critical. We removed the scleral buckle in seven cases (47%), when the use of prisms was impracticable because the angle of deviation was too great. Removal of a circumferential sponge three months after its insertion had no effect at all on one patient (case 15); in another (case 7) the removal of a wide radial sponge under the superior rectus muscle after 18 months allowed elevation of the eye, eliminating the

large vertical muscle imbalance. We see no practical advantage in waiting to remove the scleral buckle once the retina is safely reattached, since early removal should minimise episcleral fibrosis. Although we cannot predict the effect of buckle removal in a particular case, we consider that this is the logical first step in corrective surgery. We were able to control diplopia by removing the scleral buckle in four of the seven cases whose diplopia could not be joined with prisms.

Diplopia persisted after buckle removal in three cases. Definitive strabismus surgery was then performed. After forced duction testing we operated first on the eye which had already been treated. We could thus divide muscle adhesions and correct the underaction of affected rectus muscles.^{13,22,31} In our small series we did not find it necessary to overcorrect the strabismus, employ marginal myotomy, or recess the conjunctiva to enhance the effect of rectus muscle recession; techniques which have all been advocated in the management of diplopia after retinal detachment surgery.^{10,12,13,21,32-34} In both patients with horizontal diplopia who required strabismus surgery (cases 13 and 15) we eliminated diplopia by operating on the eye which had not been buckled. This confirms that strabismus surgery for this condition may be performed on either eye.^{5,27,31} In one patient (case 15) we used an adjustable suturing technique with excellent results to achieve an early and accurate restoration of fusion.^{27,28,35}

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Disseminated aspergillosis in a patient with ocular reticulum cell sarcoma

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SUMMARY A 75-year-old healthy woman developed uveitis and chorioretinal infiltrates OD compatible with reticulum cell sarcoma. She was admitted to hospital 18 months later with somnolence and confusion. Examination revealed diffuse white matter hypodensity on computed tomography and a persistent cerebrospinal fluid pleocytosis. At necropsy reticulum cell sarcoma was found in the right globe and *Aspergillus fumigatus* was present in almost every other organ, including the brain.

Disseminated aspergillosis occurs most commonly in immunocompromised patients.^{1,2} We report a case of disseminated aspergillosis in a patient with reticulum cell sarcoma (RCS) restricted to one globe.

Case report

A 75-year-old woman was in good health until June 1982, when she developed "floaters" OD and was found to have bilateral posterior uveitis with a fundus appearance thought most compatible with birdshot choroidopathy (Fig. 1). Examination revealed a positive purified protein derivative (PPD) test, negative syphilis serology, and normal toxoplasma and histoplasmosis titres. Her visual acuity declined to 20/200 OD by July 1983 despite topical steroids and one periocular injection of Depo-Medrol (methylprednisolone acetate) 60 mg. The patient refused diagnostic vitrectomy. She became confused and had difficulty ambulating in December, 1983, and was admitted to hospital for evaluation.

She was somnolent and disorientated to time and place with a temperature of 101° F (38.3°C). On general physical examination she was otherwise normal. Her visual acuity was no light perception OD and light perception OS. Neurological examination showed moderately depressed level of consciousness and symmetrically increased flexor tone. Chest x-ray,

complete blood count, biochemical profiles, arterial blood gasses, erythrocyte sedimentation rate, antinuclear antibody, complement levels, VDRL, cryptococcal antigen, and toxoplasma antibody titres were normal. Fever resolved with hydration. Brain CT showed diffused deep white matter hypodensity and a lucent area in the left thalamus thought to be a lacunar infarct (Figs. 2A, B). The lumbar puncture opening pressure was normal, and the cerebrospinal

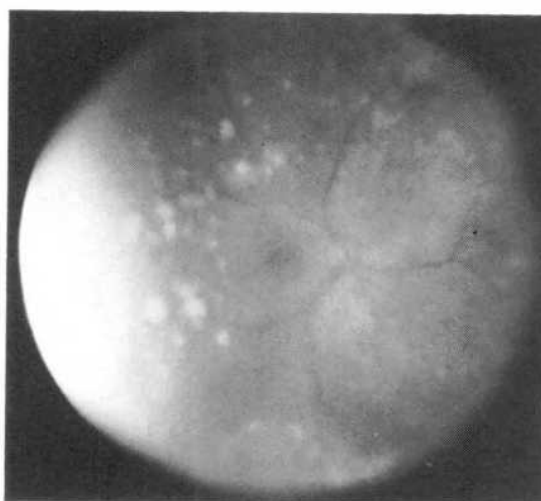


Fig. 1 Fundus photograph OD of multiple small, yellow lesions in the posterior pole and retinal periphery involving the inner choroid and retina.

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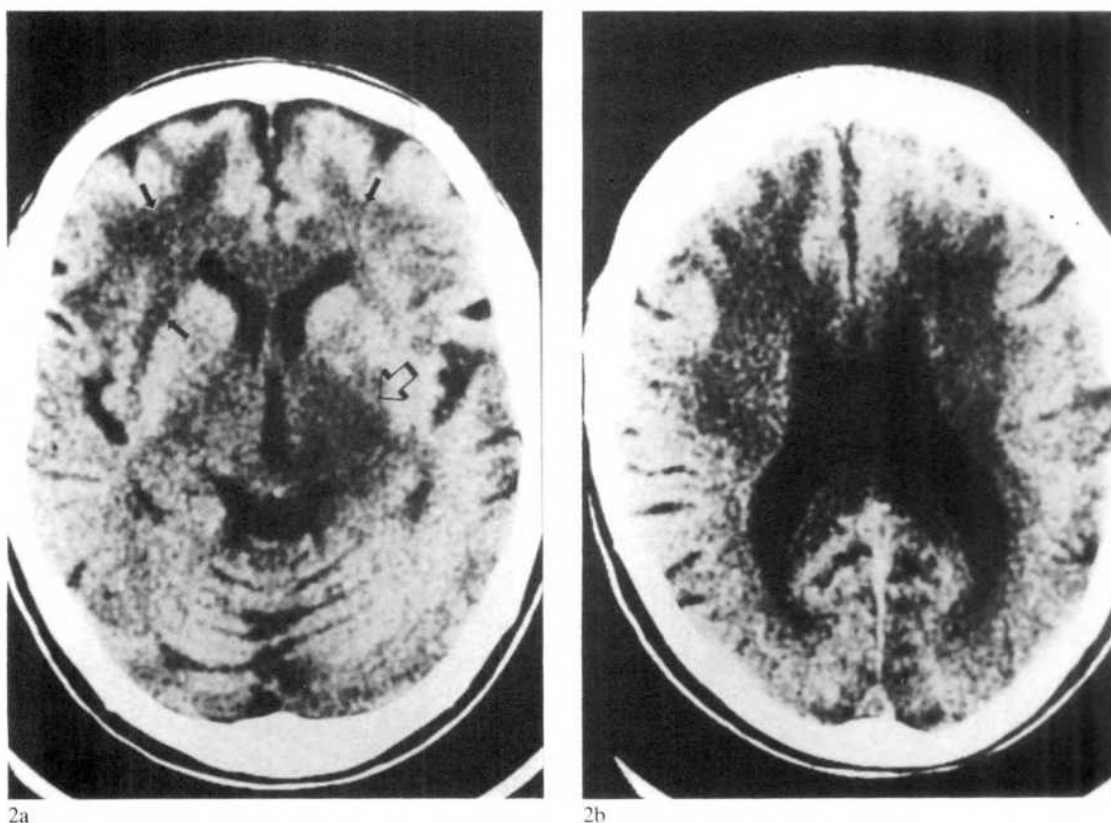


Fig. 2 CT scan of brain without contrast: (a) at level of thalami showing hypodense area in left thalamus (open arrow) without mass effect (thought initially to be a lacunar infarct) and frontal white matter hypodensity (small arrows); and (b) at level of lateral ventricles showing diffuse white matter hypodensity without other focal lesions. Patient's left is on right.

fluid was normal except for 13 leucocytes, predominantly lymphocytes. Cytological examination showed only reactive lymphocytes. CT scans of the retroperitoneum and bone marrow biopsy were normal. Two additional lumbar punctures revealed a persistent lymphocytic pleocytosis with normal protein and glucose and no evidence of malignant cytology.

Decadron (dexamethasone) 6 mg intravenously six hourly and isoniazid 300 mg were started after 10 days in hospital because of progressive obtundation. Pars plana vitrectomy and chorioretinal biopsy OD two days later showed reticulum cell sarcoma (Figs. 3A, B), and whole brain irradiation was begun with the presumptive diagnosis of lymphomatous meningitis. After three weeks in hospital she developed a fever and a large left pyopneumothorax. The pleural fluid leucocyte count was in excess of 100,000, mostly polymorphonuclear leucocytes, and cultures grew *Staphylococcus aureus*. The patient died one week later despite antibiotic treatment.

Pleural fluid cultures grew *Aspergillus fumigatus*

one week after death. Post-mortem examination revealed invasive aspergillus in lungs, adrenals, oesophagus, colon, heart, kidneys, lymph nodes, skeletal muscles, pancreas, thyroid, parathyroids, and spleen. There was diffuse invasion of the cerebral white matter by aspergillus, and a large left thalamic abscess cavity was filled with branching septate hyphae (Figs. 4A, B). No primary source of aspergillus was found in the lungs or paranasal sinuses. The globes showed necrotic reticulum cell sarcoma cells OD and invasion of the choroid and retina by fungus OS with microabscesses but without evidence of tumour. The remainder of the necropsy, including mediastinal and retroperitoneal dissection, failed to reveal systemic lymphoma. An incidental thyroid carcinoma was restricted to one thyroid nodule.

Discussion

Disseminated aspergillosis occurs most commonly in immunocompromised hosts, although it can occur

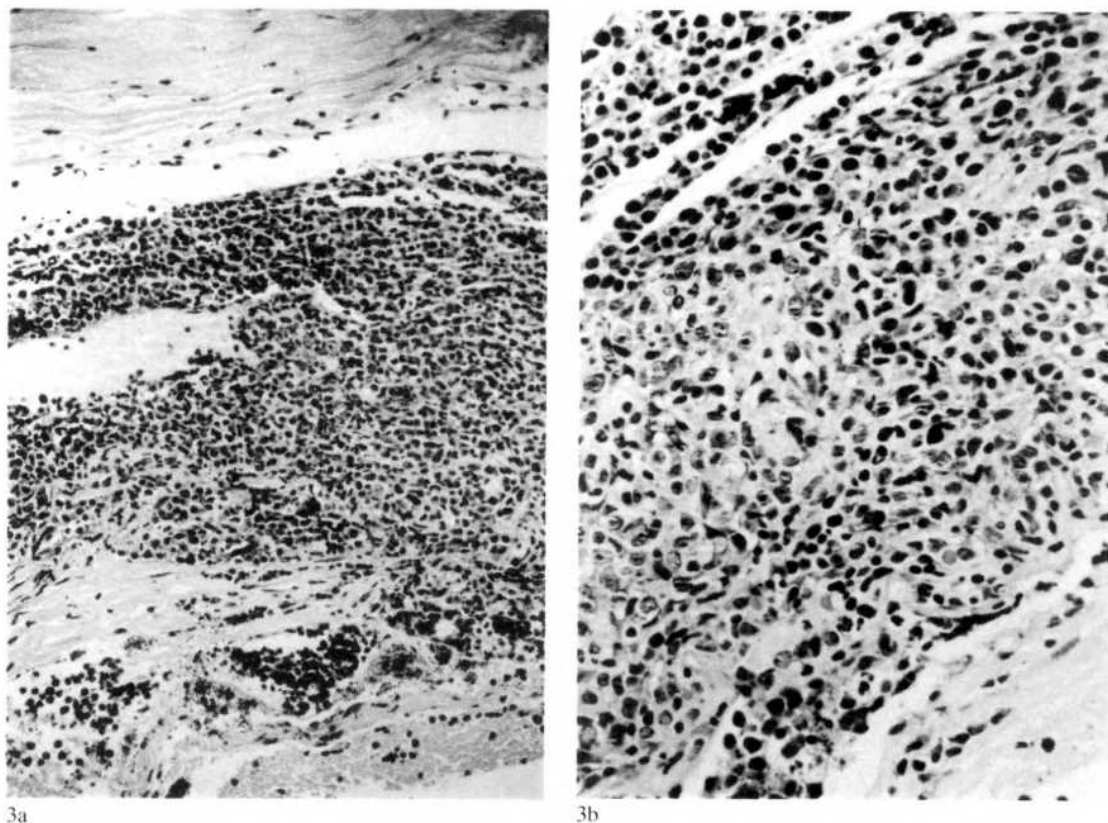


Fig. 3 Eye wall biopsy: (a) tumour infiltrating retina, choroid, and sclera; and (b) malignant cells with abundant cytoplasm and large, irregular, convoluted nuclei with prominent nucleoli. Immunohistochemistry (T200) was positive for lymphocyte antigen; kappa, lambda, and S-100 were negative.

rarely in patients thought to be otherwise normal.^{3,5} It is notoriously difficult to diagnose, because cultures are frequently unreliable⁶ and serological testing is not yet widely available.^{7,8} *Aspergillus* typically invades cerebral blood vessels, causing ischaemic lesions and abscesses. Aspergillosis of the central nervous system may be suspected clinically after the apoplectic onset of focal neurological deficits in a febrile, immunocompromised patient with pulmonary infiltrates.⁹ CT findings usually consist of low absorption areas with minimal mass effect and slight contrast enhancement. The cerebrospinal fluid (CSF) is frequently normal but may contain a modest lymphocytic pleocytosis or raised protein concentration.

Ocular reticulum cell sarcoma usually presents in patients middle-aged or older as a chronic uveitis involving the posterior segment more than the anterior segment and is variably responsive to steroids. The disease involves both eyes in 80%¹⁰ and the central nervous system (CNS) in more than 50% of

reported cases.¹¹ CNS symptoms include personality changes, changes in level of consciousness, and focal neurological deficits. Brain CT in patients with ocular and CNS reticulum cell sarcoma usually shows contrast enhancing parenchymal masses with surrounding oedema. The CSF cytology was positive in 25% to 50% of these patients.¹¹

This patient with ocular reticulum cell sarcoma was presumed to have lymphoma involving the CNS. In fact, the sarcoma was limited to the right globe while *aspergillus* was found in almost every other organ, including the left globe. The site of *aspergillus* entry is uncertain, because the initial chest x-ray was normal and the patient had no sinus disease at post-mortem examination. Chest x-rays are normal in 15% to 20% of patients with invasive pulmonary aspergillosis,^{1,12} and terminal pulmonary involvement by *aspergillus* implies that our patient probably had radiologically inapparent pulmonary disease at the time of admission. Patients with impaired granulocyte function due to hereditary disorders, myeloprolifer-

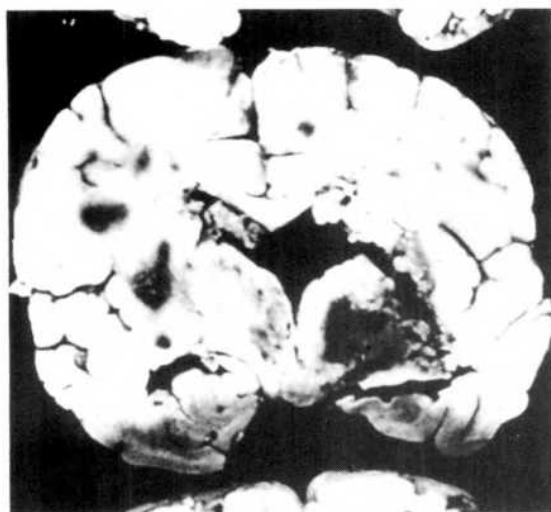


Fig. 4(a) Coronal sections of gross brain (patient's left on right) with abscess cavity in left thalamus and multiple smaller areas of ischaemic damage located throughout deep white matter.

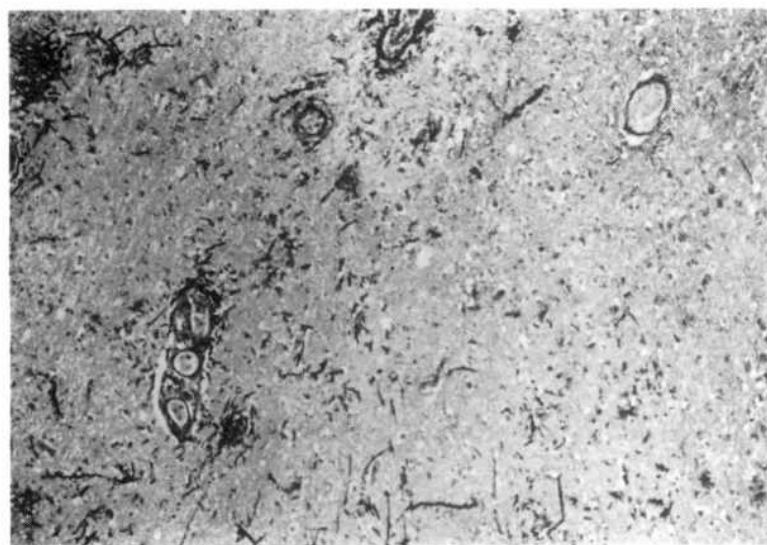


Fig. 4(b) Section stained with Grocott fungal stain showing white matter tissue necrosis and branching hyphae penetrating blood vessel walls into surrounding brain.

ative disease, or immunosuppressant therapy are most at risk for aspergillus infections.^{13,14} Granulocyte function was not specifically tested in our patient, but she was not granulocytopenic in hospital, she had no history of recurrent bacterial infections, she had a normal bone marrow examination, and she had never received chronic immunosuppressant or antibiotic therapy. A defect in cell mediated immunity associated with focal lymphoma should not have affected resistance to ubiquitous fungi. One previous case of ocular reticulum cell sarcoma died with disseminated

nocardiosis, but this patient was probably immunosuppressed after receiving six months' oral prednisone therapy in modest doses.¹⁵

It is unlikely that this patient had these two very uncommon diseases by chance, and it may be that patients with ocular reticulum cell sarcoma are at increased risk of local or disseminated infections with aspergillus or other opportunistic organisms. The therapeutically important distinction between CNS lymphoma and CNS aspergillosis may be difficult when other clinical clues are absent, for both processes can cause obtundation, focal neurological deficits, and CSF lymphocytic pleocytosis. The onset of neurological symptoms is most commonly sudden in CNS aspergillosis and gradual in CNS lymphoma, although this distinction was not helpful with the patient reported here. Brain CT showed hypodense areas corresponding to aspergillus invasion and abscess and may have been the best premorbid indication of disseminated aspergillosis.

The authors thank Dr Nancy L. Harris and Dr John J. Brooks for help with immunohistochemistry.

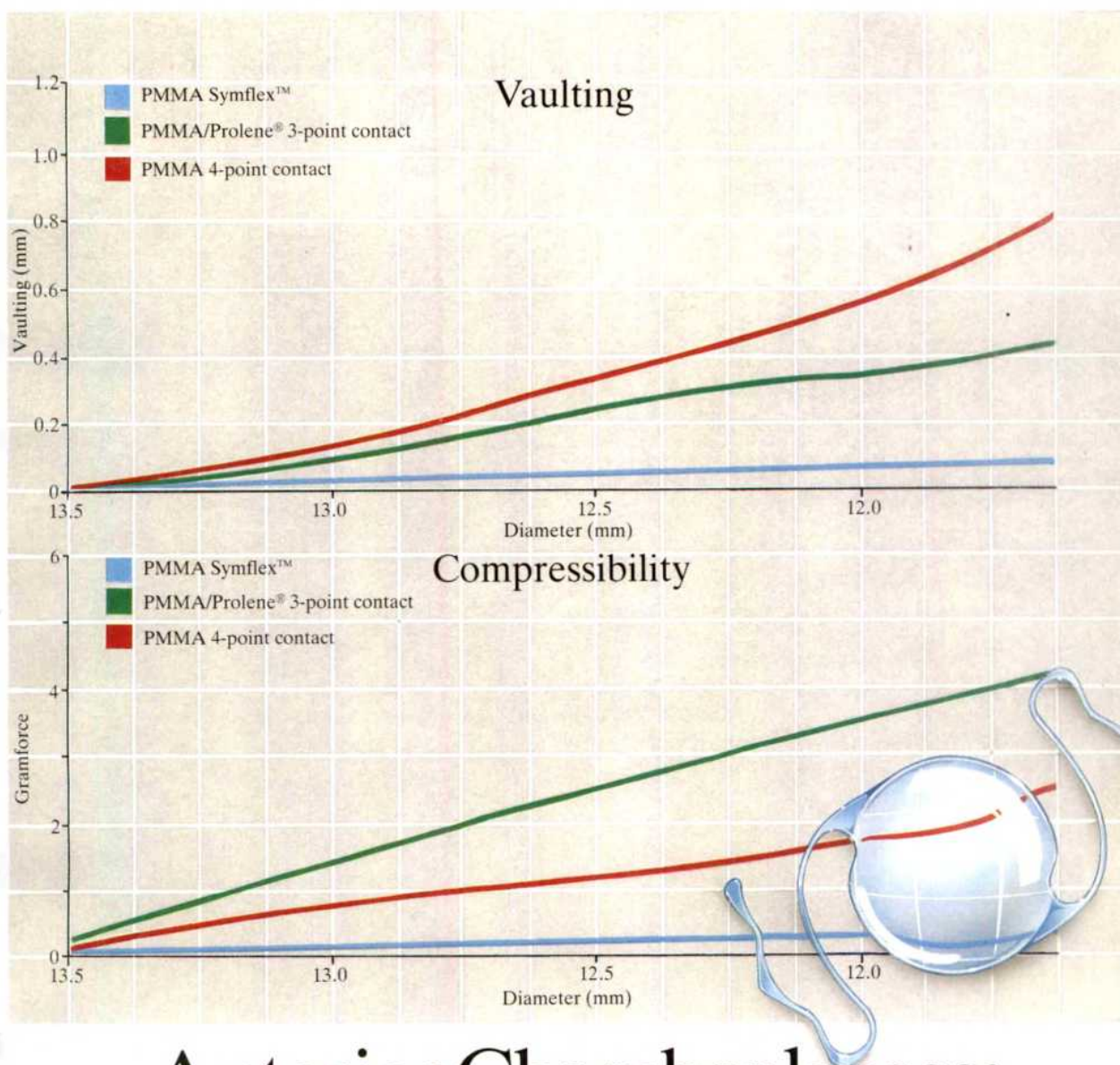
Dr Folberg is currently with the Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, Iowa, and Dr Kaufman is at the Massachusetts Eye and Ear Infirmary, Boston, Mass.

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Leber's hereditary optic neuropathy: mitochondrial and biochemical studies on muscle biopsies

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SUMMARY Two patients with Leber's hereditary optic neuropathy underwent morphological and biochemical investigations of muscle biopsy samples from the biceps brachii. Although clinically there was no muscle weakness or atrophy, specific histochemical and electron microscopic examinations showed mild but distinct myopathic changes, including abnormal oxidative enzyme activities, aggregates of enlarged mitochondria in the subsarcolemmal regions, and disruptions of myofilaments. Biochemical analyses of mitochondria isolated from muscle samples did not show any deficiency in respiratory-chain enzyme complexes or defect in content of cytochromes. Leber's hereditary optic neuropathy is assumed to be a multisystem disorder involving skeletal muscle also.

Leber's hereditary optic neuropathy is a rare condition characterised by rapid loss of central vision presenting as acute optic neuritis. Both eyes are involved, with or without an interval, and visual prognosis is usually poor owing to secondary optic atrophy. The disease generally affects healthy young adults, though mild neurological symptoms and signs are occasionally present. The mode of inheritance long remained a puzzle, but detailed pedigree analyses in recent decades have suggested a non-Mendelian cytoplasmic form of inheritance. The aetiology is still uncertain, but abnormal phenotypic expression of the gene is thought to require an interaction with yet undefined extrinsic or environmental factors.¹⁻⁵

Recent evidence for maternal transmission of a human mitochondrial genome prompted us to study muscle biopsy specimens obtained from patients with Leber's hereditary optic neuropathy with reference to the morphology and biochemistry of muscle mitochondria. This paper reports preliminary results indicating mitochondrial changes associated with mild myopathic processes.

Materials and methods

Two patients with Leber's hereditary optic neuro-

pathy were subjects for morphological and biochemical studies of muscle biopsies.

CASE REPORTS

Case 1. A 16-year-old male, a healthy high school student, had a sudden blurring of the left vision with no preceding illness, when he was said to suffer from acute optic neuritis. Four months later he experienced an acute blurring of the right vision and was referred to us for investigations. On examination the corrected visual acuity was 0.04 OD and finger counting at 10 cm OS, with dense central scotomas. Motilities, ocular anterior segments, and media were normal except for sluggish pupillary reactions. Ophthalmoscopy revealed hyperaemia and swelling of the right optic disc and temporal pallor of the left optic disc, with otherwise no remarkable change. He was given a large dose of corticosteroids, and in a few weeks the acute inflammatory changes of the right optic disc subsided but the vision did not recover. The bilateral severe visual loss with large central scotomas remained during over six months' follow-up. There was a definite family history of optic nerve disease. A brother was examined and found to have suffered from bilateral poor vision due to optic atrophy, reporting that he had experienced episodic visual loss in childhood. The parents were healthy and not consanguineous.

Case 2. A 19-year-old male was referred to us for investigation of bilateral poor vision since the age of

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15 years. At that time he had sudden loss of vision without preceding general illness in the right eye initially and with intervals of nine months in the left eye. On examination the corrected visual acuity was 0.02 OD and 0.01 OS, with sluggish pupillary responses and large central scotomas. Motilities were normal, and the ocular anterior segments and media were also normal. Ophthalmoscopy revealed generalised pallor of both optic nerve heads. There was a family history of optic nerve disease; the patient's mother and a maternal uncle had long suffered from bilateral visual loss due to optic atrophy following acute optic neuritis.

Neither patients had any other symptoms than the visual failure. Physical and routine laboratory studies, including examination of the cerebrospinal fluid, gave normal results. Neurological examinations revealed no abnormality. In case 1 the forearm exercise test showed a normal rise of blood lactate and pyruvate levels.

MORPHOLOGY AND BIOCHEMISTRY OF MUSCLE BIOPSIES

Muscle biopsies were obtained under local anaesthesia from the left biceps brachii muscle, in case 1 during the acute inflammatory phase of the disease and in case 2 at the atrophic stage. Separate samples were processed for histochemistry, electron microscopy, and mitochondrial biochemistry.

For the histochemical and histological studies, the muscle biopsy specimens were rapidly frozen, and cryostat sections were processed with a battery of histochemical stains and examined with a light microscope. Morphological details were studied with haematoxylin and eosin and the Gomori modified trichrome stains. Mitochondrial oxidative enzyme activity was examined by the NADH-tetrazolium

reductase reaction (NADH-TR). Other histochemical studies included the adenosine triphosphatase (ATPase), acid phosphatase, oil red O, and periodic acid Schiff (PAS).

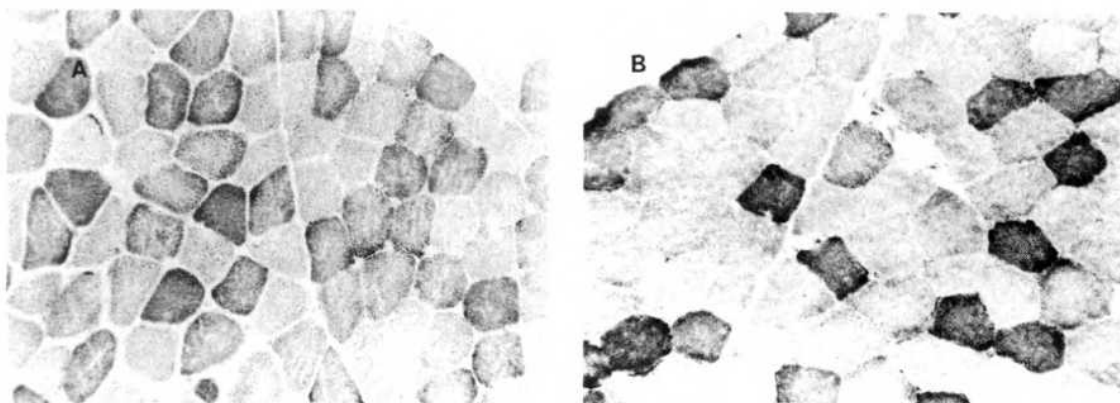
For the electron microscopic studies the muscle samples were fixed in 3% glutaraldehyde in 0.125 M cacodylate buffer, pH 7.4, for 2 h, rinsed in the cacodylate buffer for 1 h, postfixed with 1% osmium tetroxide for 1 h, dehydrated in a graded series of ethanol, and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined with a JEOL 100-B electron microscope.

For the biochemical analysis mitochondria were isolated from frozen muscle biopsies by the method of Bookelman *et al.*⁶ Mitochondrial respiratory enzyme complexes were assayed by measuring NADH-dehydrogenase, rotenone-sensitive NADH cytochrome c reductase, succinate cytochrome c reductase, cytochrome c oxidase, and citrate synthase. Reduced-minus oxidised spectra of cytochromes were recorded at room temperature in a Shimadzu UV-3000 dual wave spectrophotometer. Cytochromes were reduced by addition of 1 mM KCN. The concentrations of cytochromes were calculated from the extinction coefficients of Bookelman *et al.*⁶ Protein concentrations in mitochondrial preparations were measured by the method of Lowry *et al.*⁷

Results

MUSCLE HISTOCHEMISTRY

Mild features of myopathic processes were observed in muscle biopsies of the two cases. The muscle fibres measured 40 to 60 μ m in cross section. There was a normal reaction to the ATPase, which revealed the usual proportion of two fibre types randomly dis-



Figs. 1 (a) and (b) Muscle biopsy: cryostat sections stained with NADH-TR, illustrating focal increase of oxidative enzyme activity in many type I fibres. No other abnormality is present with two fibre types distributed in a checkerboard pattern. A: case 1, B: case 2.

tributed in a checkerboard pattern. There was no increase in numbers of internal nuclei or increase of the endomysial connective tissue. With the modified trichrome stain a minimal amount of haematoxylin-positive material reacting red was scattered in the subsarcolemmal regions. With the NADH-TR stain numerous type I fibres showed either a focal increase or decrease in oxidative enzyme activity (Figs. 1A, B). The intracellular glycogen content demonstrable with the PAS stain was normal. In addition in case 1 there was a moderate increase in the intracellular lipids demonstrable with the oil red O. In case 2 there was a mild increase in the acid phosphatase reaction.

MUSCLE ELECTRON MICROSCOPY

Electron microscopic examination of the muscle biopsies showed mild myopathic changes in the two cases. In case 1 the central area of some muscle cells was involved by disruption of myofilaments, with Z band streaming, resembling central core disease. A few muscle fibres had nemaline rods which showed the characteristic periodicities arranged in a rectangular lattice. The sarcoplasm of occasional fibres

contained cytoplasmic bodies consisting of unusual deposits characterised by a central dark region containing Z band material and a peripheral zone made up of thin filaments extending outwards in a ray-like fashion (Fig. 2). Large numbers of enlarged mitochondria were clustered beneath the sarcolemma of some fibres (Fig. 3). Similar myopathic changes were observed in case 2, with noticeable subsarcolemmal collections of enlarged mitochondria and focal disruptions of myofilaments. In addition a few fibres had tubular aggregates beneath the sarcolemma (Fig. 4).

MITOCHONDRIAL BIOCHEMISTRY

Quantitative assays of respiratory-chain enzyme complexes in isolated mitochondria were carried out in the two cases, and the results are illustrated in Table 1, in which control data from 10 normal subjects are also tabulated. In case 1 NADH dehydrogenase, rotenone-sensitive NADH, cytochrome c reductase, succinate cytochrome c reductase, and citrate synthase were markedly increased by twofold to threefold of the mean value of the normal, with a

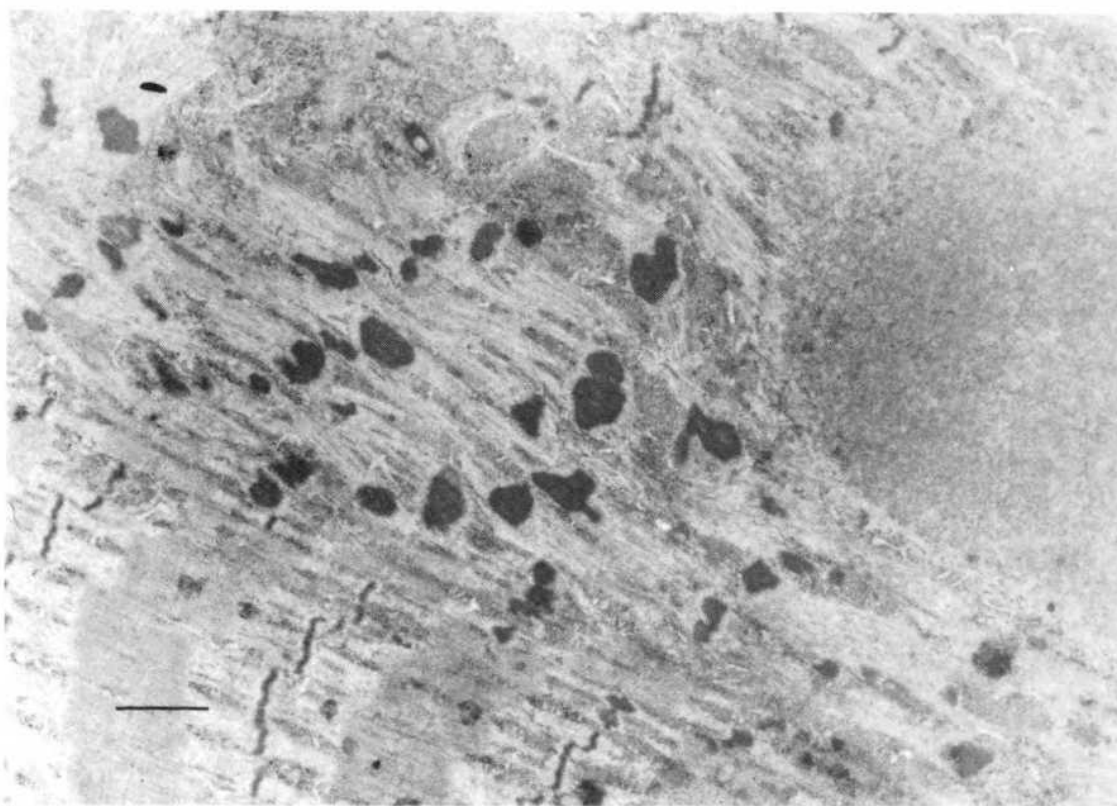


Fig. 2 Muscle biopsy (case 1): electron micrograph illustrating presence of nemaline rod and cytoplasmic body with disrupted myofilaments. Bar = 1 μ m.

Fig. 3 Muscle biopsy (case 1): electron micrograph illustrating aggregates of enlarged mitochondria in the subsarcolemmal region. Bar = 1 μ m.

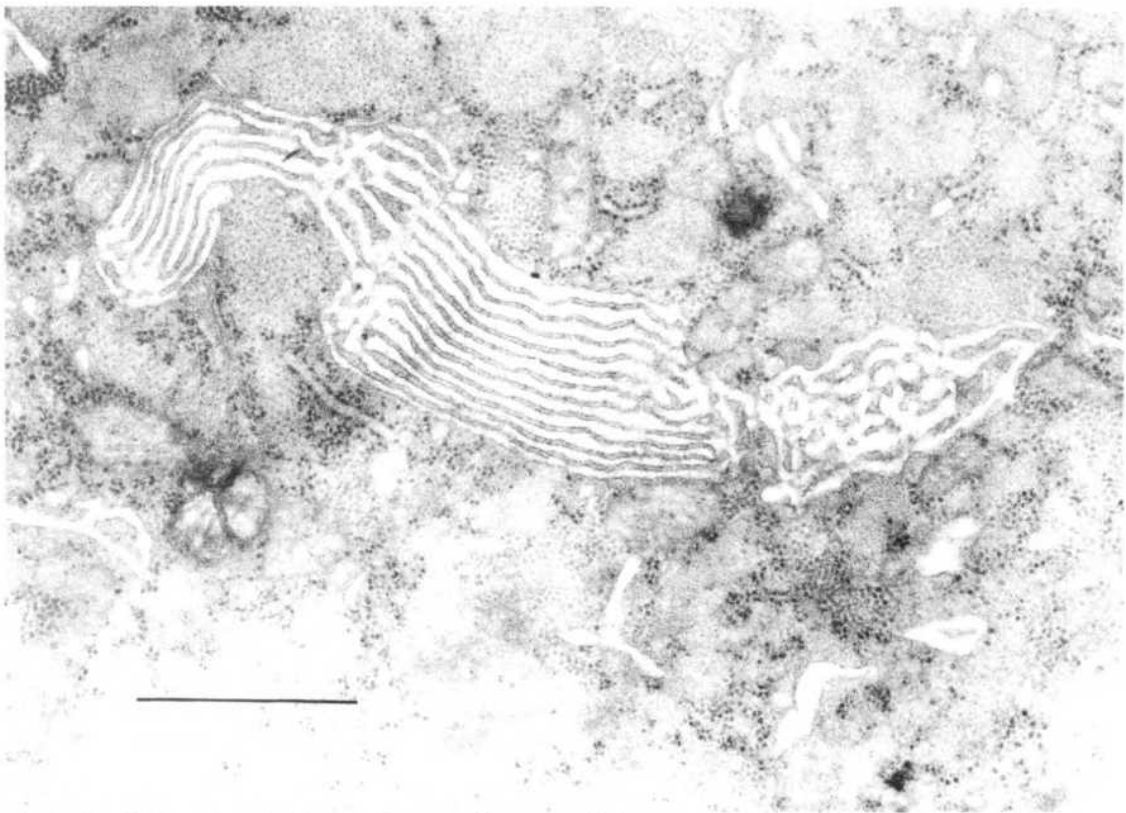
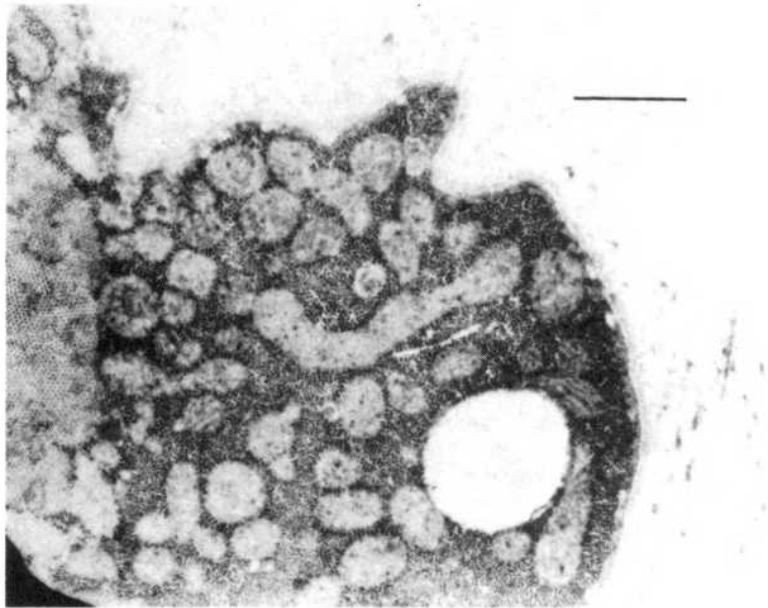


Fig. 4 Muscle biopsy (case 2): electron micrograph illustrating tubular aggregates in the sarcolemma. Bar = 1 μ m.

Table 1 Enzyme activity in muscle mitochondria*

Enzymes	Case 1	Case 2	Controls†
NADH dehydrogenase	5.59	2.49	2.11 ± 1.58
NADH cytochrome c reductase	0.431	0.167	0.201 ± 0.098
Succinate cytochrome c reductase	1.02	0.357	0.321 ± 0.118
Cytochrome c oxidase	1.58	1.85	1.58 ± 0.800
Citrate synthase	1.39	0.298	0.380 ± 0.147

*Expressed as $\mu\text{mol}/\text{min}/\text{mg}$ mitochondrial protein.†Mean $\pm$ SD in 10 normal subjects.

‡Rotenone sensitive activity determined as differential activity in the presence and absence of rotenone in the reactive mixture.

Table 2 Content of cytochromes in muscle mitochondria*

Cytochromes	Case 1	Case 2	Controls†
a + a ₃	659	519	550 ± 167
b	668	511	504 ± 122
c + c ₁	686	852	615 ± 258

*Expressed as pmol/mg mitochondrial protein.†Mean $\pm$ SD in 10 normal subjects.

normal level of cytochrome c oxidase. In case 2 all these enzymes were within the normal range.

The contents of mitochondrial cytochromes calculated from reduced-minus oxidised spectra are illustrated in Table 2. It can be seen that both cases had a normal concentration of mitochondrial cytochromes.

Discussion

The clinical picture in these cases, together with the familial occurrence of the disease, is in all respects consistent with Leber's hereditary optic neuropathy. The morphological studies of muscle biopsy specimens showed mild but distinct myopathic changes in the two cases examined, in that some of the fibres had noticeably abnormal reactions to a battery of histochemical stains—in particular the modified trichrome and NADH-TR—and also ultrastructural changes including nemaline rods, cytoplasmic bodies, and subsarcolemmal collections of enlarged mitochondria. These histochemical and electron microscopic abnormalities are found in case of congenital or acquired myopathies of various causes but not in normal persons.^{8,9}

A variety of neurological and psychiatric symptoms and signs, including spasticity, gait disturbance, abnormal tendon reflexes, and hearing loss, are known to occur in association with Leber's optic neuropathy. Post-mortem studies also reveal widespread involvement of the central nervous system. These systemic disorders are usually so mild that they remain asymptomatic or unrecognised unless looked for specifically, though overt manifestations resemble

ing arachnoiditis or multiple sclerosis may occur in occasional patients.^{1,5} The present observations indicate involvement of the skeletal muscle as part of the disease, characterised by mild myopathic processes that are evident histologically but not clinically. This previously unreported findings favours the view that Leber's optic neuropathy is not confined to the optic nerve but represents a multisystem disease.^{4,5} The condition might be termed optico-encephalomyopathy.

The most notable feature of Leber's optic neuropathy is its unique hereditary pattern. There is now a fair amount of evidence suggesting that inheritance follows not Mendelian law but a pattern compatible with mitochondrial transmission. There are no recorded cases of paternal transmission, and the majority of daughters—virtually all daughters in thoroughly studied families—of patients and carriers become carriers. These phenomena are reasonably explained by maternal transmission.¹⁰⁻¹² Furthermore, there is recent evidence for maternal transmission of the human mitochondrial genome, and many subunits of respiratory-chain enzyme complexes have been shown to be encoded by mitochondrial DNA. It is therefore possible to develop a working hypothesis that several diseases with non-Mendelian maternal transmission pattern result from inheritance of an abnormal mitochondrial genome.^{13,14}

Two points in the present observations warrant discussion in line with the above hypothesis. First, type I fibres showed red staining material reacting to the modified trichrome stain in the subsarcolemmal regions, and the stained areas appeared to contain clusters of abnormally enlarged mitochondria at the electron microscopic level. These pathological features, together with the focal increase of oxidative enzyme activity revealed by the NADH-TR stain, are comparable to the ragged red fibres which have been known to occur in mitochondrial myopathy or mitochondrial cytopathy, a diverse group of muscle and/or nerve diseases characterised by structurally or numerically abnormal mitochondria and/or abnormally functioning mitochondria.^{15,16} Furthermore, the enlarged mitochondria in the subsarcolemmal regions may conform to the recent report that subsarcolemmal mitochondrial profiles are significantly larger in cases of Leber's optic neuropathy than in control cases.¹⁷ It seems that myopathic changes characterised by the ragged red fibres are considerably less prominent in Leber's hereditary optic neuropathy than in typical mitochondrial cytopathy. Secondly, as regards the functional aspects of muscle mitochondria in Leber's optic neuropathy, no deficiency of cytochromes or respiratory-chain enzyme complexes was detectable in the two cases examined. Rather, case 1 showed two- to threefold enhancement of the mito-

chondrial enzyme complexes. One possible explanation for the apparently enlarged and hyperactive mitochondria is a compensation for yet undefined metabolic defect. It should, however, be emphasised that the present results do not entirely exclude the possibility of a deficiency of many other mitochondrial DNA-encoded enzymes or proteins.

The pathogenesis of Leber's hereditary optic neuropathy is unknown, but a fault in cyanide metabolism has been suggested. Recently a pronounced reduction in the activity of the enzyme thiosulphate sulphur transferase (rhodanese) was reported in liver samples from patients with the condition.¹⁶ This mitochondrial matrix enzyme detoxifies cyanide by a reaction with thiosulphate to form thiocyanate and sulphate. However, this finding has not been confirmed in muscle samples from patients with Leber's syndrome.¹⁷

Further studies on mitochondrial pathology in Leber's hereditary optic neuropathy are needed to elucidate its underlying metabolic defect.

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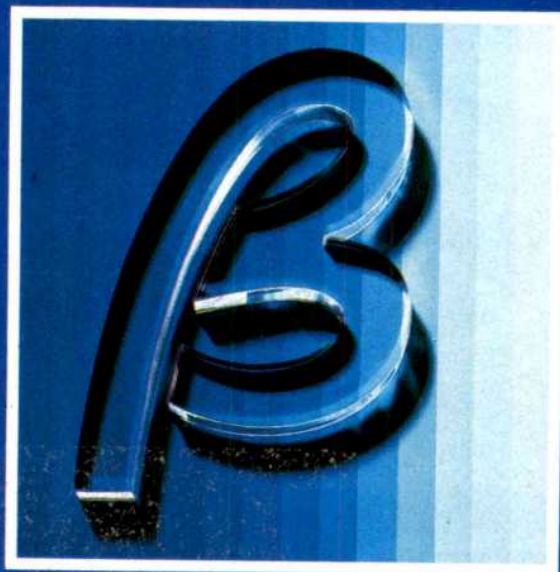
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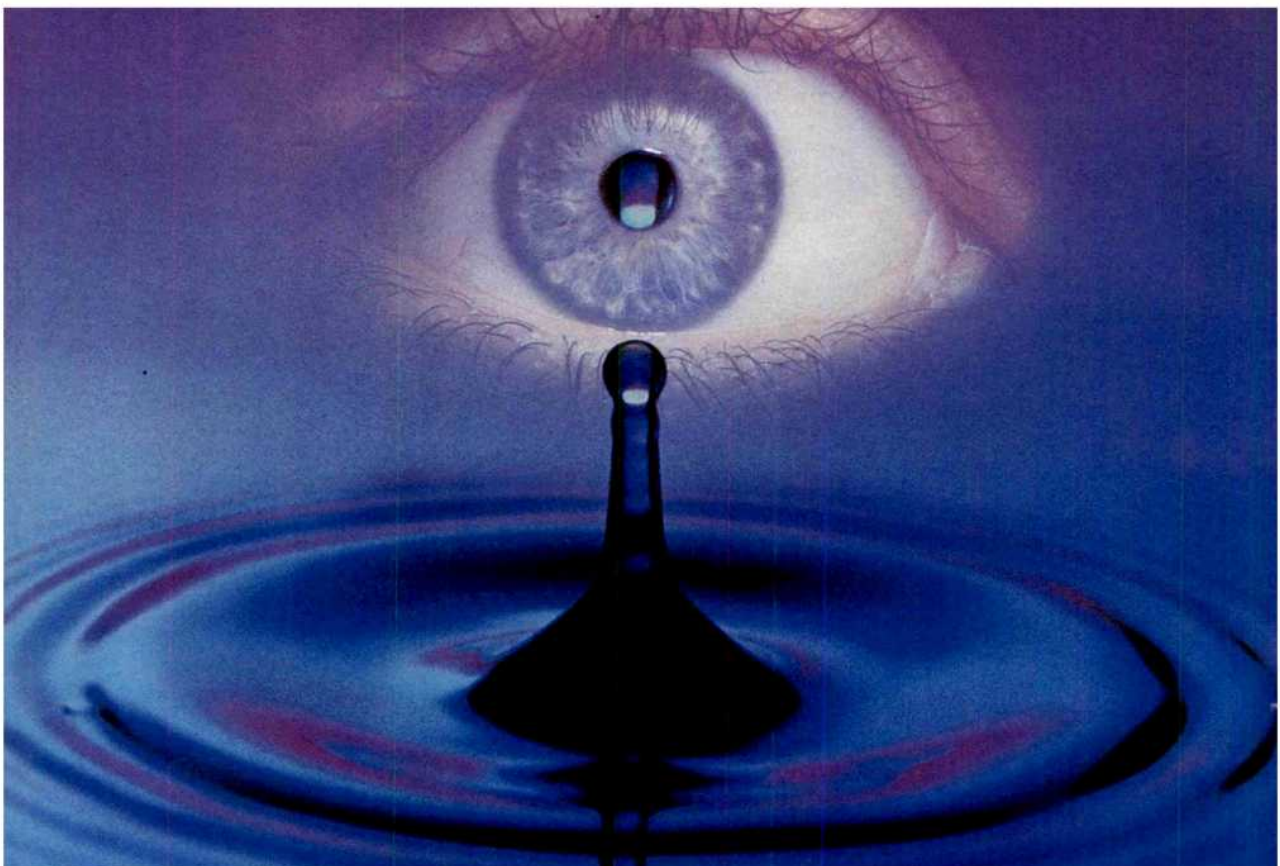
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Optic disc drusen and episodic visual loss

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SUMMARY A case is reported in which recurrent episodes of visual loss occurred over a period of 26 years in a patient with bilateral optic disc drusen. Visual field loss was associated with episodes of ischaemic optic neuropathy. The possible mechanism is discussed.

Optic disc drusen may be associated with arcuate scotomas, constriction of the peripheral visual field or rarely the loss of central vision. The progression of visual field defects is usually insidious.¹ There are reports of ischaemic optic neuropathy occurring with drusen, but these have been solitary events.^{2,3} This report documents recurrent episodes of visual loss occurring over a period of 26 years in a patient with optic disc drusen.

CASE REPORT

The patient was a 54-year-old right handed woman with a history of recurrent episodes of painless visual loss.

She first presented to the National Hospital in 1966 with a seven-year history of field loss in her left eye and a 10-day history of blurred vision in her right eye.

A general examination gave normal results. An ophthalmic examination found visual acuities right

6/6 and left 6/24. The visual fields showed extensive nasal loss on the left side and a full right field (Fig. 1). Nerve fibre loss was noted on the left disc, and there were optic disc drusen. On the right disc there were buried drusen and the inferior part of the disc was swollen with distended neurones, cotton-wool spots, and superficial haemorrhages.

X-rays of the skull and optic foramina, bilateral carotid angiograms, and an air ventriculogram were normal.

In 1970, 1976, 1978, and 1981 she had recurrent episodes of visual loss and on each occasion she was found to have optic disc swelling. Treatment with corticosteroids apparently improved visual function. She was first seen by one of us in 1981. Visual acuities were right 6/18 and left 6/60. Visual fields showed extensive loss on the left and diffuse constriction on the right. There were drusen superonasally on the right disc and numerous drusen on the left. A computed tomographic scan of the orbit and brain showed no intracranial lesion and normal sized optic nerves (Fig. 2). It was concluded that the disc drusen

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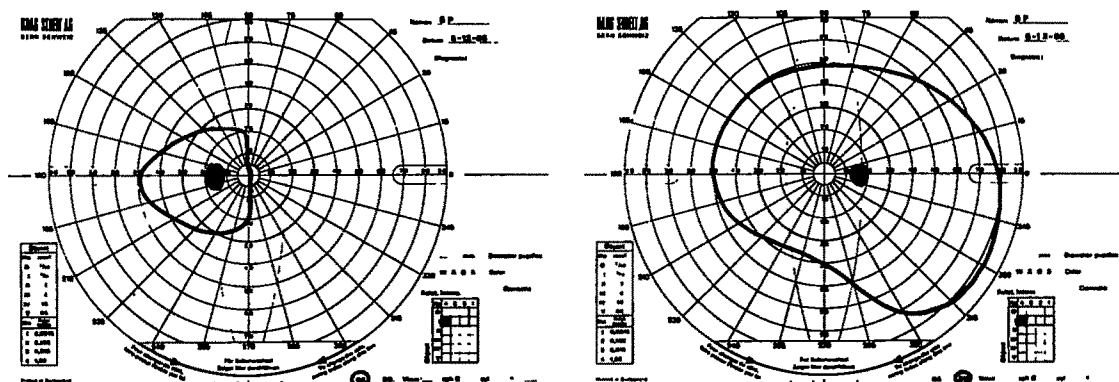


Fig. 1 Visual fields showing extensive nasal loss on the left and normal right field.



Fig. 2 Computerised tomographic scan of orbit showing normal optic nerves, and left drusen.

were associated with recurrent episodes of ischaemic swelling of the optic nerves.

Over the next four years she had three further episodes of visual loss, in the right eye in 1984 and 1985 and in the left eye in 1985. She was treated with corticosteroids during each episode.

When seen by us in December 1985 visual acuities were right 6/9, left counting fingers. Further constriction of the visual fields had occurred (Fig. 3). Examination of the discs showed bilateral optic disc drusen (Fig. 4).

Discussion

Optic disc drusen consist of calcified, laminated aggregates of extracellular material. Recent ultrastructural studies by Tso⁴ and Spencer⁵ have indicated that drusen form as a result of alterations in axoplasmic transport at the disc producing accumulations of axoplasmic material.

The association between optic disc drusen and visual field defects is common. In a large study Lorentzen found field defects in 87% patients with drusen,⁶ but it is rare for optic disc drusen to be associated with loss of central vision, and it has been argued that this occurrence should prompt further investigation for another cause.¹

The mechanism by which optic disc drusen produce field loss is uncertain. The visual field defects do not correspond to the position of the drusen on the disc. The acute onset of field defects suggests a vascular event. Circulation of the disc may be disturbed by optic disc drusen, because the vascular supply is anomalous, predisposing towards optic disc haemorrhage or ischaemic optic neuropathy. Optic disc drusen are commonly found in discs with an anomalous vascular pattern, especially an increased number of arterial or venous branches.⁷ Several reports have drawn attention to the occurrence of haemorrhage and ischaemic optic neuropathy with

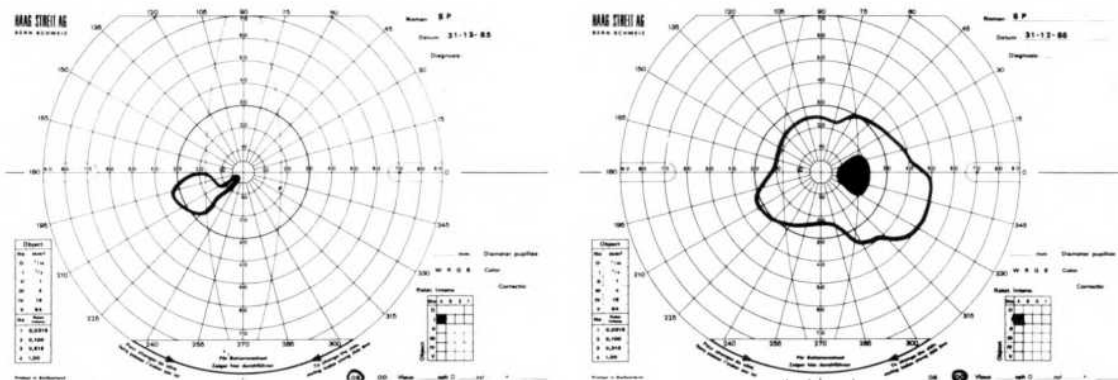


Fig. 3 Visual fields showing constriction of both visual fields.

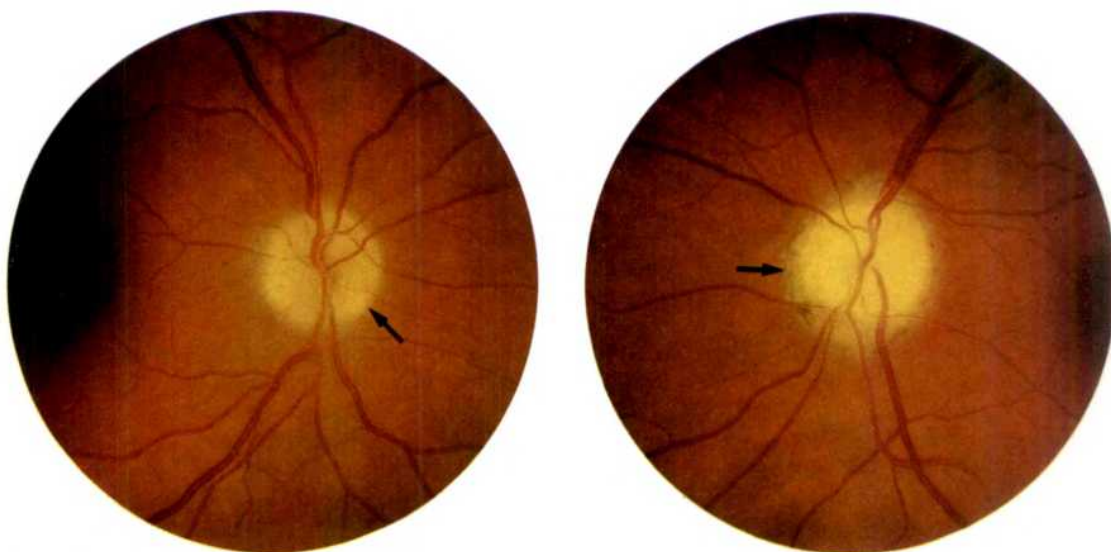


Fig. 4 Optic discs showing disc drusen (arrowed).

arcuate field loss and segmental disc pallor. This has been noted in four patients with optic disc drusen.⁸

The circulation of the disc with drusen may also be more vulnerable because the disc is small. Recently an association has been established between optic disc drusen and an abnormally small disc.⁹ It is well recognised that there is an increased likelihood of ischaemic optic neuropathy occurring in small discs.¹⁰

In our patient with optic disc drusen it is probable that the recurrent episodes of visual loss were due to periods of relative vascular insufficiency producing ischaemic optic neuropathy. The rationale for treatment with corticosteroids during each episode of visual loss was to reduce additional damage caused by neuronal swelling.¹¹ Firm evidence is lacking that this treatment improved visual function, but it is of interest that she still retained 6/9 vision in one eye despite numerous episodes of visual loss.

We are indebted to Miss Josephine Lace for secretarial assistance and Mr Richard Dewhirst for the illustrations.

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Quantification of macular ischaemia in sickle cell retinopathy

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NEAL S PEACHEY, JOSE G CUNHA-VAZ, AND MORTON F GOLDBERG

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SUMMARY Macular ischaemia has a central role in the pathophysiology and prognosis of retinal macular disease. We attempted to quantitate two of its major components as follows: vascular non-perfusion, by measuring the foveal avascular zone (FAZ), using fluorescein angiography; and functional damage, using automated perimetry of the central 30°. Sickle cell disease was chosen for study because it was considered a prototype for a purely ischaemic retinopathy without an exudative component. We found that the FAZ measurement was reproducible and that the patients with maculopathy had statistically larger FAZs than the normal controls ($p = 0.016$, Wilcoxon rank sum test). In addition, scotomas measured by visual field perimetry were significantly larger in the sickle cell patients with maculopathy than in those without maculopathy. Our results showed that angiography and perimetry of the central 30° were more sensitive tests for the detection of ischaemic macular disease than visual acuity and that macular ischaemia could be quantified by their use.

Retinal vascular disease has two major pathophysiological processes: alteration of the blood-retinal barrier (BRB), as reflected by capillary leakage, and ischaemia, as manifested by vascular closure.¹ Leakage has been measured quantitatively with vitreous fluorophotometry by Cunha-Vaz *et al.*^{2,3} and others.⁴ Although vascular closure throughout the fundus has been demonstrated with widefield angiography in studies by Shimizu *et al.*⁵ and Niki and co-workers,⁶ the methodology is not yet available to quantify such closure accurately.

Visual field testing has been used to measure functional damage from retinal disease in diabetes and branch vein occlusions^{7,8} in an attempt to correlate dysfunction with the amount of damage from capillary non-perfusion.

We studied patients with sickle cell disease, which is considered a prototype for purely ischaemic retinopathy. A recent investigation⁹ showed that the BRB was normal in sickle cell patients with background retinopathy as measured by fluorescein leakage on vitreous fluorophotometry; leakage was evident only when peripheral neovascularisation was also present.

We applied both fluorescein angiography and visual field perimetry to quantify vascular closure and retinal tissue function in sickle cell patients with and without observable maculopathy and in normal controls.

Materials and methods

PATIENTS

We reviewed the medical records of 186 consecutive patients being followed up in the Sickle Cell Eye Center and recruited those patients with ophthalmoscopic evidence of the macular depression sign¹⁰ or angiographic evidence of arteriolar occlusion in the macular. Eyes that had undergone prior laser photocoagulation, cryotherapy, or intraocular surgery were excluded. All patients had electrophoretic confirmation of SS, SC, SA or S-thalassaemia haemoglobin. Patients with a visual acuity worse than 20/50, cloudy media (that is, cataract, vitreous debris), glaucoma, unrelated retinal disease such as diabetes or sarcoidosis, or an unrelated cause for a visual field defect were excluded. Of 40 patients who had macular disease as defined above, 10 (group A) met our criteria for this study. The test eye had the more severe retinopathy of the two eyes.

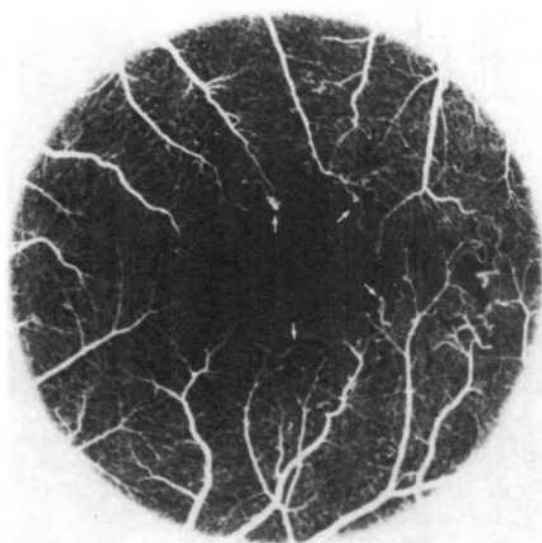


Fig. 1 Fluorescein angiogram of left eye of 46-year-old SC patient (group A, case 10). The longest diameter of the FAZ is 1.42 mm. Note irregularity of outline and terminal occlusions (arrows). Visual acuity is 20/20.

We selected another 20 eyes of sickle cell patients with no evidence of macular disease either on ophthalmoscopic examination or by angiography. We divided the 20 eyes into one group of 10 (group B) which underwent angiography and a second group of 10 (group C) which underwent perimetry. One eye of

one patient whose other eye was included in group A (patient 4, Table 1) was included in group B (patient 5, Table 2). In all other cases only one eye was tested in any patient. The eye with the most severe retinopathy was chosen. Groups B and C were matched with group A for age (see Tables 1, 2, 3). Comparisons were then made of the foveal avascular zone (FAZ) between groups A and B and of the visual fields between groups A and C.

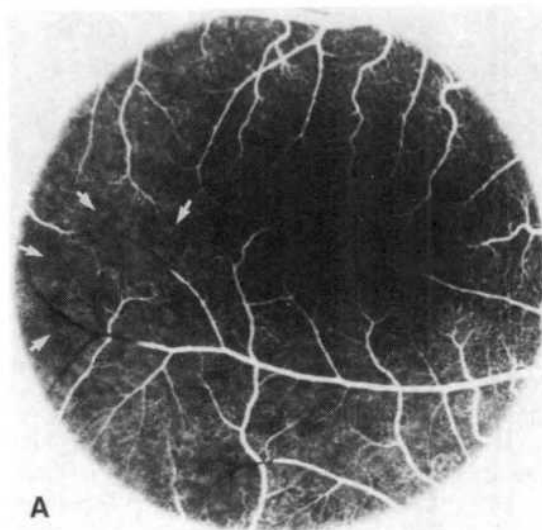
The right eyes of six age-matched hospital employees, two black and four white, without evidence of systemic or ophthalmological disease and with haemoglobin AA were selected as normal controls for the angiography. Informed consent was obtained from all participants.

FLUORESCIN ANGIOGRAPHY

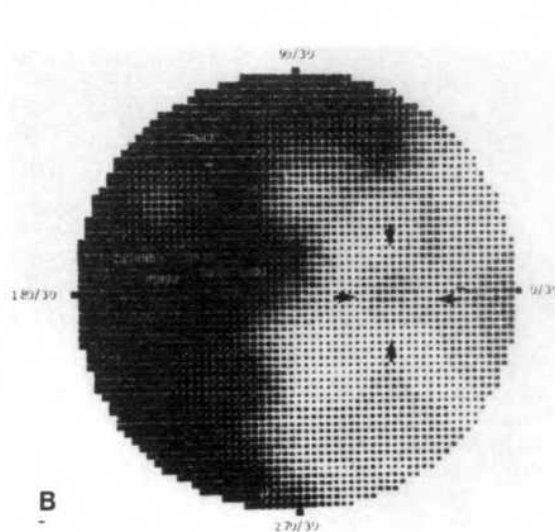
Fluorescein angiography of the macular region was performed with a 30° Zeiss fundus camera after a rapid intravenous injection of 5 ml of 10% sodium fluorescein through an antecubital vein followed immediately by a 5 ml normal saline flush.

Groups A and B and the six normal controls also underwent repeated angiography six months later to assess the reproducibility of this technique.

The negative of the angiographic frame having the highest resolution of the fovea was projected, the outline of the FAZ was drawn on a transparent overlay, and the longest diameter was measured (Figs. 1, 2A). Two of us (CML and HCC) drew and measured the FAZ of each angiogram twice in a



A



B

Fig. 2 (a) Fluorescein angiogram of right eye of 32-year-old SS patient (group A, case 6). The longest diameter of the FAZ is 0.58 mm. Note paucity of capillaries close to terminal arterioles and evidence of occlusion just temporal to fovea with surrounding areas of capillary drop-out (arrows). Visual acuity is 20/20. (b) Visual field shows large scotoma. Blind spot as marked by arrows.

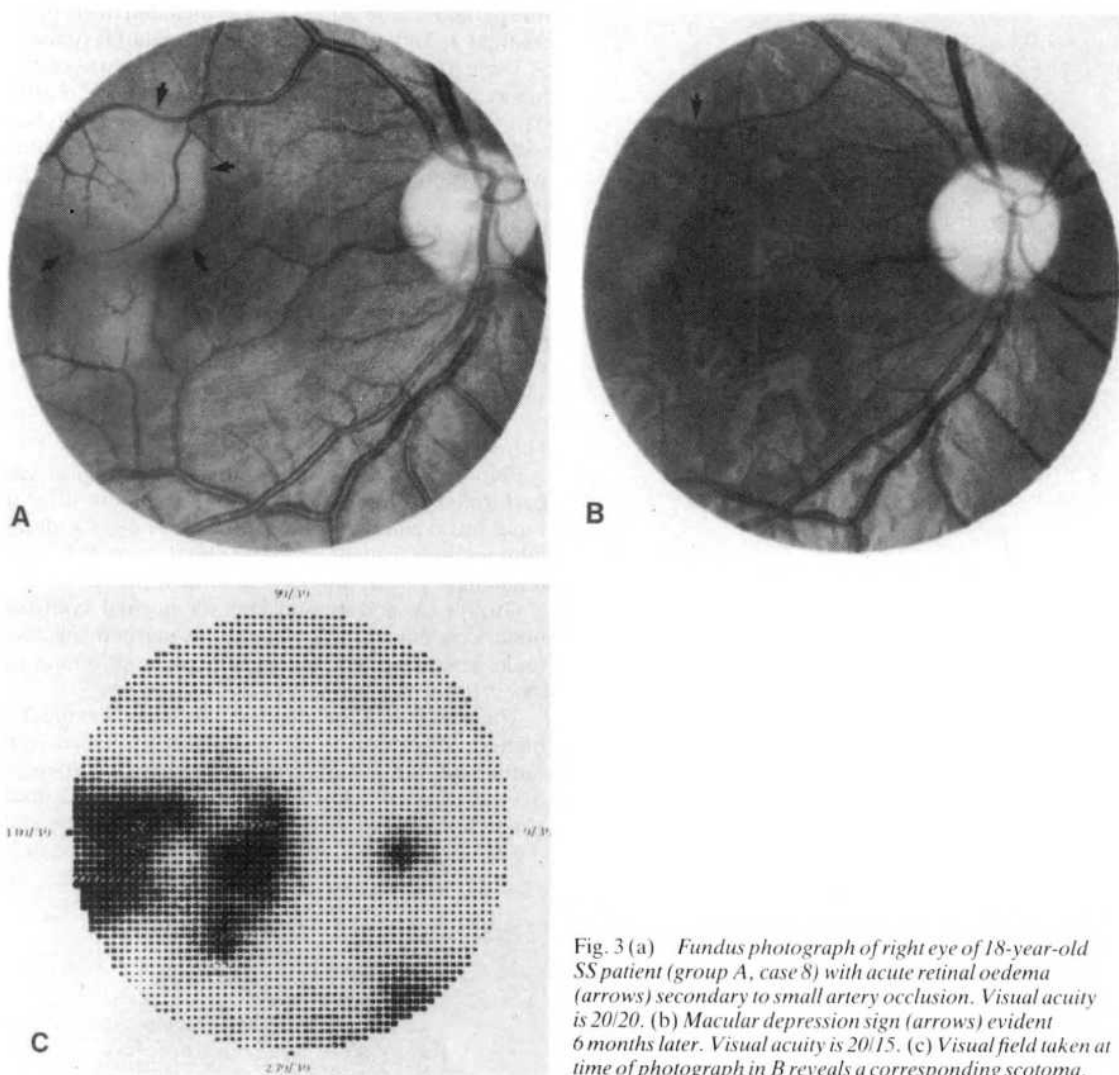


Fig. 3 (a) Fundus photograph of right eye of 18-year-old SS patient (group A, case 8) with acute retinal oedema (arrows) secondary to small artery occlusion. Visual acuity is 20/20. (b) Macular depression sign (arrows) evident 6 months later. Visual acuity is 20/15. (c) Visual field taken at time of photograph in B reveals a corresponding scotoma.

masked fashion. Less than 10% intra- or interobserver variability in these measurements allowed us to use the average among the numbers.

VISUAL FIELDS

Automated static perimetry of the central 30° of the visual field was performed with Program 33 on the Octopus perimeter (Figs. 2B, 3C). This yielded 6° of resolution between points, with a total of 73 locations tested; fast bracketing was utilised. Sensitivity depression above 4 decibels (4 db) was considered abnormal for each spot. Groups A and C underwent visual field testing.

Five different values were considered. (1) A scotoma was defined as any defect of two or more

adjacent points with a threshold depression of 4 db or greater, excluding the expected blind spot. We defined the largest scotoma as the greatest number of contiguous scotomatous points. (2) Average sensitivity depression was calculated by dividing the cumulative threshold depression in the largest scotoma by the number of points composing it. (3) The total number of defects was determined by adding all scotomatous points in the total visual field. (4) The average sensitivity depression of this value (point 3) was calculated in the same fashion as point 2. (5) The total field sensitivity depression was obtained by dividing the cumulative threshold depression of all scotomatous points by the total number of tested locations (73).

Table 1 Group A: Eyes of sickle cell patients with maculopathy who underwent fluorescein angiography and Octopus perimetry

Patient no.	Sex	Age (yr)	Haemoglobin type	Stage of retinopathy*	Visual acuity	Foveal avascular zone longest diameter (mm)
1	M	26	SS	II	20/30	0.71
2	M	36	SC	III	20/25	0.83
3	F	31	SC	III	20/20	0.68
4	F	30	STh	II	20/20	0.71
5	M	45	SS	III	20/20	0.89
6	F	32	SS	III	20/20	0.58
7	F	26	STh	III	20/30	0.80
8	M	18	SS	I	20/15	0.43
9	F	35	SC	II	20/20	1.0
10	F	46	SC	IV	20/20	1.42

*Goldberg.¹¹

Table 2 Group B: Eyes of sickle cell patients without maculopathy who underwent fluorescein angiography

Patient no.	Sex	Age (yr)	Haemoglobin type	Stage of retinopathy*	Visual acuity	Foveal avascular zone longest diameter (mm)
1	M	31	SS	II	20/50	0.80
2	F	37	SS	III	20/20	0.61
3	M	58	SC	III	20/30	0.86
4	F	14	SC	III	20/15	0.49
5	F	30	STh	III	20/20	0.55
6	F	34	STh	I	20/25	0.64
7	F	29	SA	III	20/30	0.43
8	M	57	SC	III	20/25	0.71
9	F	35	SC	II	20/20	0.80
10	F	31	SC	III	20/20	0.86

*Goldberg.¹¹

Table 3 Group C: Eyes of sickle cell patients without maculopathy who underwent Octopus perimetry

Patient no.	Sex	Age (yr)	Haemoglobin type	Stage of retinopathy*	Visual acuity
1	M	14	SS	I	20/20
2	F	30	STh	III	20/20
3	F	37	SS	III	20/20
4	M	25	STh	I	20/20
5	M	18	SS	I	20/15
6	F	45	SC	I	20/20
7	M	46	SS	I	20/20
8	M	30	SS	I	20/15
9	F	24	STh	III	20/15
10	F	33	STh	III	20/50

*Goldberg.¹¹

Results

PATIENTS PROFILE

Group A comprised eyes with maculopathy that underwent both angiography and perimetry. The patients' mean age was 32.5 years (range 18 to 46

Table 4 Foveal avascular zone: longest diameter (mm), mean $\pm$ SD

Normal controls (n=6)	Group B, without sickling maculopathy (n=10)	Group A, with sickling maculopathy (n=10)
0.52 $\pm$ 0.11	0.68 $\pm$ 0.17	0.81 $\pm$ 0.27
NS p=0.016		

Table 5 Visual field defects in sickling maculopathy

	Group A, with maculopathy (n=10) mean (range)	Group C, without maculopathy (n=10) mean (range)	Level of significance
Worst scotoma, no. of defects	19.2 (2.0-68.0)	0.9 (0-3.0)	p<0.01
Average sensitivity depression (db)	12.9 (3.2-22.2)	6.5 (0-18.0)	p<0.03
Total no. of defects	24.7 (5.0-68.0)	2.2 (0-8.0)	p<0.01
Average sensitivity depression (db)	12.9 (8.2-20.3)	6.4 (0-18.0)	p<0.01
Total field sensitivity depression (db)	4.6 (0.5-16.3)	0.4 (0-2.0)	p<0.01

See 'Materials and methods' for definitions of parameters.

years). Four patients were male and six were female; all had a visual acuity equivalent to or better than 20/30 (see Table 1).

Group B contained eyes without maculopathy that underwent angiography. The patients ranged from 14 to 58 years in age (mean 35.6 years). Three patients were male and seven were female. Only one had a visual acuity of 20/50; the remaining nine had visual acuities equivalent to or better than 20/30 (see Table 2).

Group C was composed of eyes without maculopathy that underwent perimetry. The patients were from 14 to 46 years of age (mean 30.2 years). Five patients were male and five were female. Only one had a visual acuity of 20/50; the other nine had visual acuities equivalent to or better than 20/30 (see Table 3).

All normal controls were in their twenties; four were female and two were male. And none had evidence of ophthalmic or systemic disease at their ophthalmic examination.

FLUORESCEIN ANGIOGRAPHY

The average of the longest diameter of the FAZ measured for the six normal controls was 0.52 mm, SD 0.11 mm (range 0.40 to 0.71 mm). Six months later all repeated angiograms could be superimposed

over the initial ones without change in the vascular pattern, confirming the reproducibility of this technique.

The average of the longest diameter of the FAZ measured in group A was 0.81, SD 0.27 mm (range 0.43 to 1.42 mm; see Table 1), as compared with 0.68, SD 0.17 mm (range 0.43 to 0.86 mm) in group B (see Table 2). The difference between the normal controls and the patients with maculopathy (group A) was statistically significant ($p=0.016$, Wilcoxon rank sum test; see Table 4). The difference was not statistically significant between the two subsets of sickle cell patients or between the normal controls and the patients without maculopathy, though the latter comparison approached significance ($p=0.06$, Wilcoxon rank sum test).

VISUAL FIELDS

All five values, (1) the largest scotoma, (2) average sensitivity depression of the largest scotoma, (3) total number of defects, (4) average sensitivity depression of point 3, and (5) total field sensitivity depression, were significantly larger in group A than in group C (Table 5).

Discussion

The dimensions of the FAZ have been studied by several investigators. Trypsin digest preparations of normal human necropsy eyes have revealed longest diameters ranging from 0.40 to 0.65 mm.¹² Measurement of the FAZ *in vivo* may be obtained using fluorescein angiography; with this technique Laatikainen and Larinkari¹³ have estimated that the mean diameter of the capillary free zone was 70.53 mm in patients under age 40 and 0.61 mm in patients over age 40. Recently Wu *et al.*¹⁴ have shown a similar age correlated enlargement of the FAZ; the mean longest diameter was 0.88 mm for 45 normal subjects ranging in age from 12 to 55 years. Bresnick *et al.*¹⁵ have correlated the size of the FAZ with the severity of capillary non-perfusion in the posterior pole; the median longest diameter was 0.80 mm in their normal controls and 0.92 mm in their diabetic patients. Conversely, Bird and Weale¹⁶ have found an avascular zone of only 0.20 mm in six subjects who visualised their retinal vasculature entoptically. The authors thought that crossing capillaries, which are often undetected by standard angiography, could be seen entoptically.

Vaso-occlusion is the precipitating event in the development of ischaemia in sickle cell retinopathy. Although the retinopathy of the sickle cell haemoglobinopathies is most frequently described in the peripheral retina, macular disease occurs in approximately 20% of cases.^{17,18} The macular area is pre-

disposed to vascular occlusion because end arterioles terminate along the horizontal raphe around the FAZ.

The significance of the FAZ with respect to visual function has been studied in relation to diabetes^{14,19,20} (Smith RT, *et al.*, paper in preparation). All but one of our subjects who underwent angiography had excellent visual acuity, and all of the patients with maculopathy had visual acuities equivalent to or better than 20/30. None had any related visual complaints, yet their FAZ was in general uneven and displayed prominent irregularities. When compared with that of the normal controls the FAZ enlargement of the maculopathy group was statistically significant. A clear demonstration of statistical significance between those patients with and without maculopathy, however, may require a larger sample size.

Technically, the use of a saline flush after fluorescein injection provided us with much clearer and crisper views of the FAZ than could be obtained by the standard technique. The reproducibility of our technique was evidenced by the ability to superimpose over the initial angiograms the follow-up angiograms at six months in our normal controls. We are confident that measurement of the FAZ with angiography is an accurate and reliable method.

We had difficulty, however, in delineating the FAZ in four of the angiograms, in which crossing vessels through larger areas of non-perfusion were seen. We considered these crossing vessels to be part of the outline of the FAZ. We may therefore have underestimated the real dimensions of the FAZ, particularly in those patients with maculopathy.

Octopus perimetry has also been used to establish the presence of non-perfusion in the peripheral retina⁷ (Charles HC, unpublished data). In one investigation 60° angiography, as compared with Octopus visual fields of the central 30° and peripheral 30° to 60°, was performed on 14 eyes with diabetes and 14 eyes with branch vein occlusion.⁷ Good correlation was observed between regional visual field changes and retinal capillary non-perfusion; prominent areas of field depression and dropout were especially pronounced in the midperiphery in diabetic retinopathy. In another study⁸ areas of non-perfusion on angiography in 163 diabetic eyes correlated well with Octopus visual field defects.

We attempted to quantify the visual field defects in our patients through several manipulations of the threshold depressions via the computerised printout. We calculated the average sensitivity depression of the largest single scotoma and the total number of scotomas to determine an approximate level of threshold sensitivity. A small, very depressed or abnormal scotoma, however, would be less abnormal

when total field sensitivity depression was calculated. The permutations performed allowed us to consider different ways of quantitating the data. Again, the sickle cell patients with maculopathy who had good visual acuity but an abnormally enlarged FAZ revealed significantly large scotomas. For each calculated value the patients with maculopathy had larger defects than those without maculopathy.

The scotomas matched well the geographic distribution of non-perfusion by angiography (Figs. 2, 3). However, the limitations of resolution in Program 33 at 6° precluded the exact superimposition of the central angiograms on the visual fields. Inasmuch as there is a learning curve associated with any psychophysical measurement and the testing situation itself is a variable process, it can be argued that a single test might not be of major importance. However, the fact that every parameter studied (that is, largest scotoma) was significantly increased in the maculopathy patients shows the data to be internally consistent, thereby supporting the value of the test.

We believe that macular ischaemia is quantifiable by the two techniques presented herein: measurement of the FAZ by angiography and assessment of the depth of threshold depression by Octopus perimetry. Since all but two of our subjects had visual acuities equal to or better than 20/30, both techniques which demonstrated anatomical and functional abnormalities appear to provide a more sensitive measurement of macular disease than visual acuity testing.

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Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine

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SUMMARY This study was undertaken to determine whether intravenous lignocaine could mitigate or prevent the ocular reactions and especially the acute increase in intraocular pressure associated with laryngoscopy and tracheal intubation. Two groups of children undergoing minor eye surgery under nitrous oxide-oxygen-halothane anaesthesia were examined. The experimental group ($n=17$) received 2 mg/kg lignocaine and the controls ($n=18$) an equivalent volume of saline. The incidence of local laryngeal and ocular reflexes was much lower in the lignocaine group. Pulse acceleration was significantly lower in the lignocaine group ($p<0.025$), and the maximal mean intraocular pressure was significantly less than in the control group ($p<0.005$). Other ocular reactions were recorded, and all were attenuated after lignocaine administration. The beneficial effects of lignocaine, a suppressant of autonomic reflexes, suggest that intraocular pressure, like the heart rate, rises after intubation as a result of autonomic stimulation. The use of intravenous lignocaine is thus recommended for children at risk, such as those needing an urgent operation because of lacerated eye injury under rapid sequence induction of anaesthesia.

Conspicuous systemic reactions accompany laryngoscopy and tracheal intubation. Previous studies have shown the ability of intravenous lignocaine to reduce these autonomic responses^{1,2} and its effectiveness as a cough suppressant.³

A brief elevation of intraocular pressure (IOP) during laryngoscopy and tracheal intubation is not harmful to the normal or even glaucomatous eye, but it may be hazardous to a lacerated and perforated globe or to the eye after recent surgery.^{4,6} Intravenous lignocaine has been found to attenuate the rise in IOP caused by tracheal intubation.⁷ The purpose of the present study is to evaluate in children the overall effects of intravenous lignocaine given prior to tracheal intubation on ocular, autonomic, and laryngeal responses.

Materials and methods

Thirty-five patients, aged 1-10 years, scheduled for minor eye surgery under general anaesthesia were included in the study. None of these children had a

history of glaucoma or intraocular disease, and they needed the operation for correction of strabismus or ptosis.

Pure inhalational anaesthetic technique was used, based on inhalation of mixture of nitrous oxide and oxygen with addition of halothane up to 2%. Five minutes after induction of anaesthesia the initial measurements of heart rate, blood pressure, and IOP were taken, and pupillary reactions (miosis or mydriasis), lacrimation, and systemic reactions such as cough and breath holding were recorded by two observers by mutual agreement. Then an intravenous injection of 0.13 ml/kg of coded solution was given in a double blind randomised manner. The solution contained either 2 mg/kg lignocaine HCl without preservative ($n=17$) or normal saline ($n=18$).

The intraocular pressure was measured with Schiøtz tonometer. The Schiøtz units were converted to mmHg by the appropriate calibration table for Schiøtz tonometry. Heart rate was recorded continuously by Mennen 741 electrocardiogram monitor and blood pressure was measured manually by sphygmomanometer.

The measured parameters were recorded 1 and 2 minutes after the injection of the coded solution.

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When the eyes were in midposition, pupils in miosis, and the mandible muscles well relaxed, tracheal intubation was performed using a non-cuffed tube and without addition of muscle relaxants. In all cases the intubation was smooth and uneventful. Immediately after intubation all measurements were repeated every minute for the next 4 minutes. Statistical analysis was performed by the Student's *t* test.

Results

Seventeen children received intravenous injection of lignocaine and 18 children received saline. In the control saline group the intubation caused a significant acceleration in the heart rate from a mean of 93.3, SEM 3.7, beats per minute to 111.7, SEM 5.3, ($p < 0.01$), while in the lignocaine group the change was non-significant, from 92.6, SEM 4.6, to 101.6, SEM 4.7, beats per minute ($p < 0.2$).

The reactions of the patients to tracheal intubation are shown in Fig. 1. At the same stage of anaesthesia these reactions were observed in nine of the 18 patients of the saline group compared with only two of the 17 patients in the lignocaine group. Of these nine patients in the control group all had pupillary dilatation, two had lacrimation, and four coughed. In the lignocaine group only one patient responded to intubation by coughing.

Figure 2 displays the intraocular pressure in the control and lignocaine groups during induction of anaesthesia and immediately after the tracheal intubation.

The mean rise of the intraocular pressure of both groups reached its peak value during the first minute

after intubation and was 18.0 mmHg, SEM 0.9, in the control group, and 14.9 mmHg, SEM 0.5, in the lignocaine group. Initial values were 12.9 mmHg, SEM 0.6, and 14.2 mmHg, SEM 0.5, respectively (difference NS). The rise at 1 minute after intubation in the saline group was statistically significant compared with its initial recording (< 0.005); however, this was not the case in the lignocaine group. The difference in peak intraocular pressure between the two groups after tracheal intubation was also statistically significant ($p < 0.005$).

Analysis of the intraocular pressures, of those patients who did not cough in the two groups showed essentially the same significant difference in pressure as shown in Fig. 2.

Discussion

During induction of anaesthesia the phase of tracheal intubation generally causes intense autonomic reflex

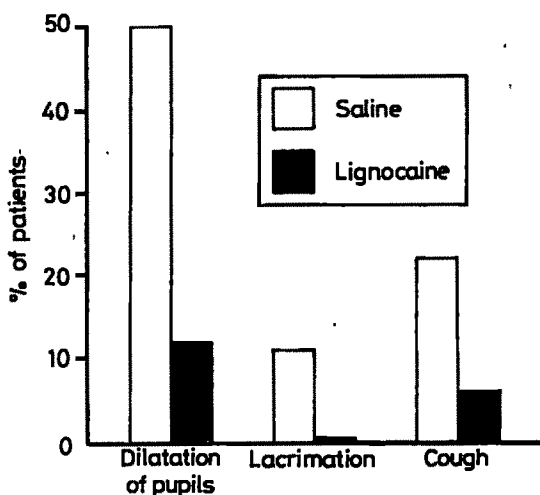


Fig. 1 Comparison of the ocular and systemic reactions to tracheal intubation in the saline versus lignocaine groups.

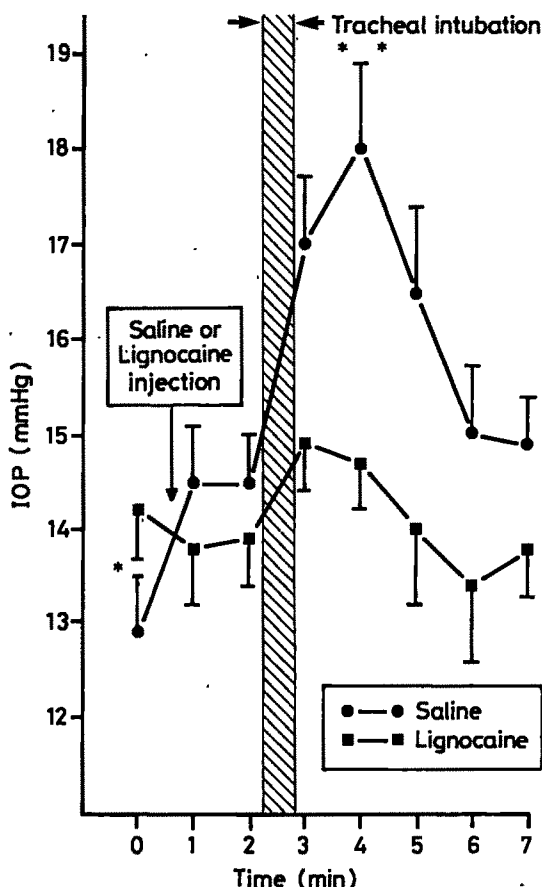


Fig. 2 Comparison of the intraocular pressure in experimental and control groups. * $p = \text{NS}$. ** $p < 0.005$.

responses such as tachycardia, hypertension, and a rise in the intraocular pressure.^{12,46} These changes, which are short lived, probably have little influence on normal healthy individuals. However, in patients suffering from a lacerated globe^{5,6} even a mild rise in IOP as a result of these autonomic responses may be dangerous, especially when rapid sequence induction of anaesthesia has to be conducted.

The mitigation of IOP responses as presented in this study, with a rise of 5.1 mmHg in the control group compared with 0.7 mmHg in the lignocaine group, may have an important implication in patients with penetrating eye injury. Attenuation of IOP responses by means of other anaesthetic agents such as fentanyl requires the administration of very high doses, which are not suitable for urgent cases and result in prolonged respiratory depression and delay in tracheal extubation.

A Schiøtz tonometer was employed owing to its ease of use and our need for relative and not absolute values of IOP. In spite of its disadvantages compared with applanation tonometry, the relative inaccuracy of the Schiøtz tonometer can be ignored in the healthy eye with average scleral rigidity and normal IOP.^{8,9}

Among the factors affecting the intraocular pressure, changes in the systemic arterial blood pressure have the lowest significance owing to displacement of aqueous from the anterior chamber, which is equilibrated by a shift of blood from the choroidal vessels.^{6,10} A direct and immediate relation exists between the central venous pressure and intraocular pressure, and the rise in central venous pressure caused by coughing is instantly transmitted to the eye by impeding the efflux of aqueous.⁶ Laryngoscopy and intubation, as shown in this study, also have an important role in raising intraocular pressure, possibly as a result of the sympathetically mediated vasoconstriction generating increased venous return and a sudden rise in central venous pressure.⁷ This suppression of ocular and cough reflexes is produced by the inhibition of polysynaptic spinal reflexes by lignocaine.¹¹

The observation of the described ocular and laryngeal reactions during induction of anaesthesia, especially as IOP is not routinely measured, will serve to indicate and alert the ophthalmologist to a possible rise in IOP during that period.

Children have brisk cardiovascular responses; they also have a higher incidence of perforating eye injury than adults. The use of intravenous lignocaine is especially indicated in this group of patients.

In strabismus surgery, a temporary decrease in IOP is observed due to manipulation of the globe during the operation, without any relation to the type of anaesthesia or to the type of muscle operated upon.¹²

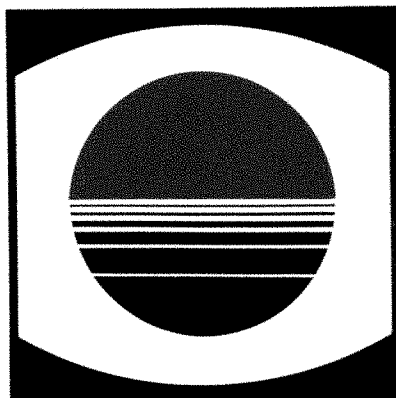
We suggest that lignocaine exerts its effect on reducing intraocular pressure by mitigating autonomic reactions. Its administration before tracheal intubation in children suffering from lacerated eye is recommended, particularly when rapid sequence induction is needed in the anaesthesia of urgent ophthalmic operations.

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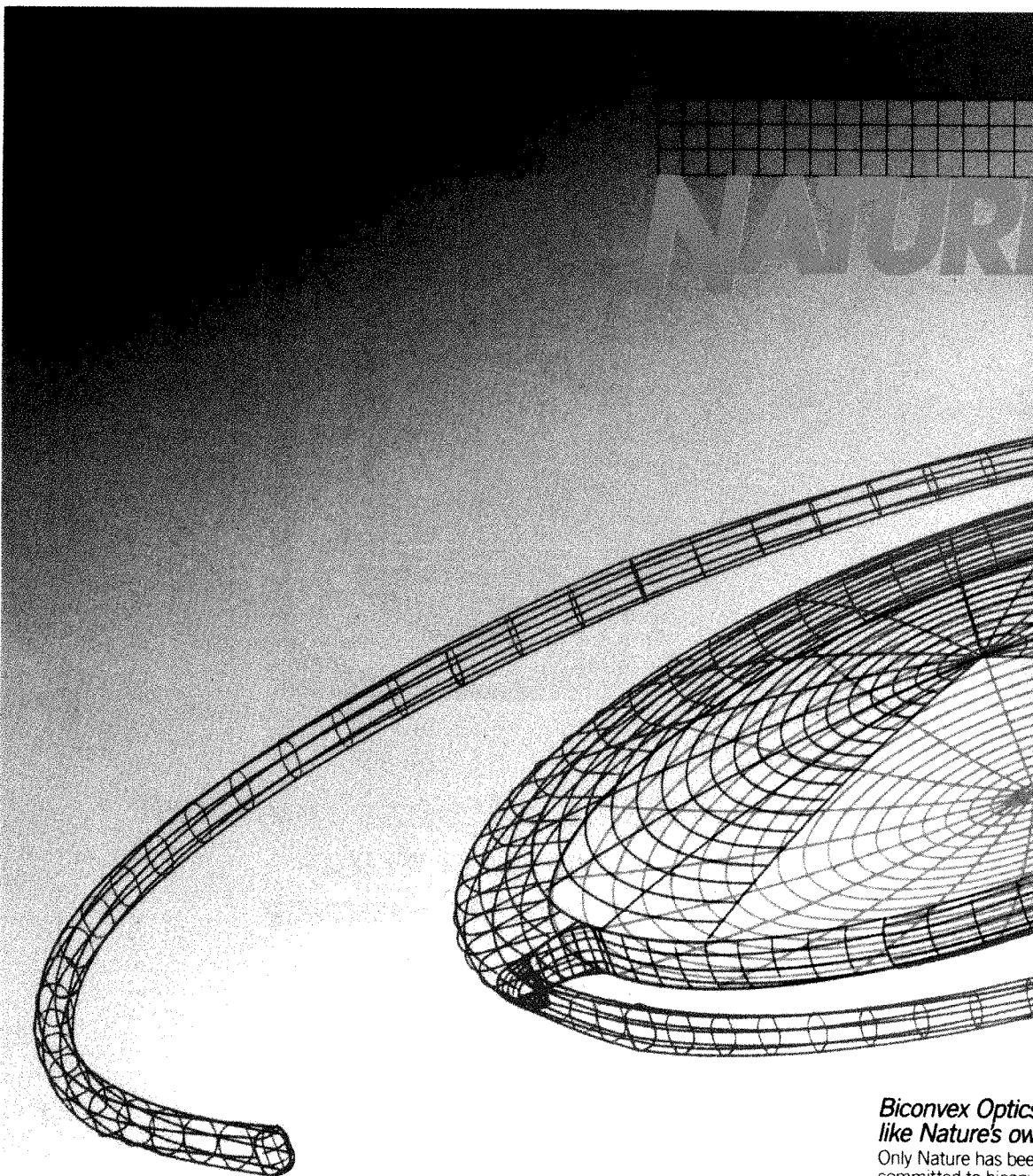


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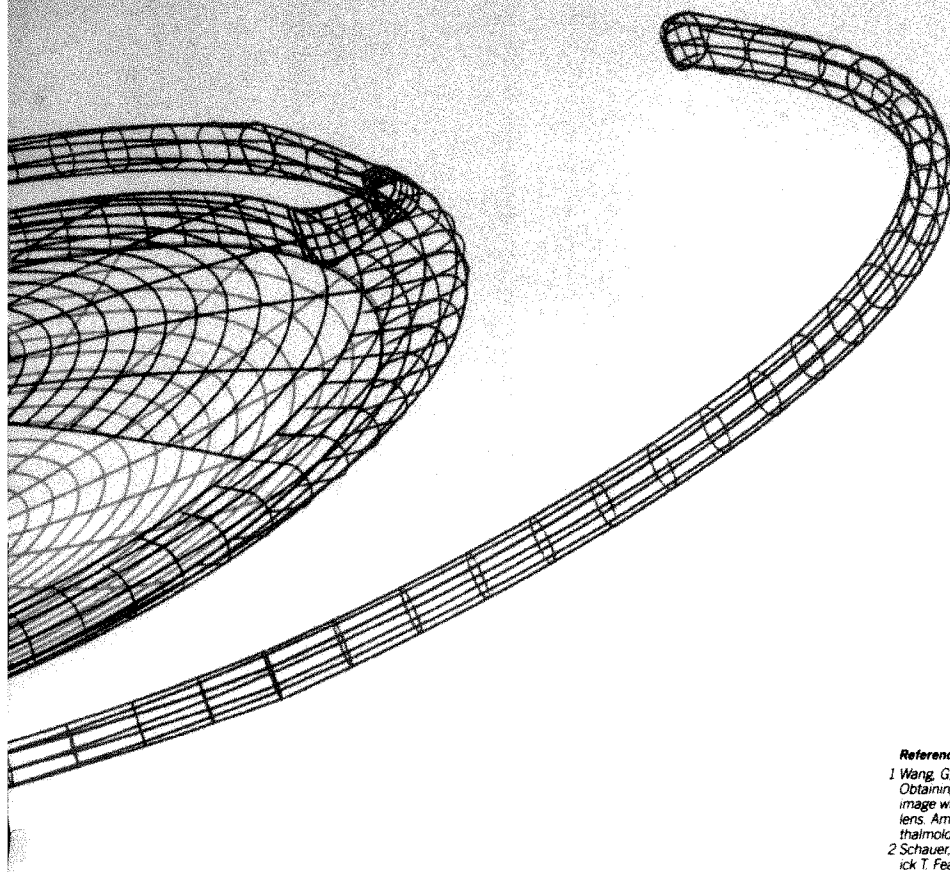
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SUMMARY Investigations were carried out to determine whether the melanin present in the blue and brown eyes were eumelanin, the melanin present in black hair and dark skin, or pheomelanin, the melanin present in red hair and the skin of people with red hair. Our results showed that UV-visible irradiation of blue or brown eye melanin did not produce any superoxide. Irradiation of ⁵¹Cr-labelled Ehrlich ascites carcinoma cells in the presence of blue or brown eye melanin did not produce significant cell lysis. The electron spin resonance (ESR) signals of blue and brown eye melanins were very similar to those of eumelanin. Comparison of these findings with our previous results indicated that the blue and brown eye melanins are essentially eumelanin. The ESR signals further suggested that in the case of both blue and brown eye melanins the iris, ciliary body, choroid, and retinal pigment epithelium did not differ.

The melanin present in the black hair and in the skin of people with black hair is called eumelanin, whereas the melanin in the red hair and in the skin of people with red hair is termed pheomelanin.¹⁻³ These melanins differ in their chemical and physical properties as well as in their biosynthetic pathways. Eumelanin is synthesised from dopa, and pheomelanin from cysteinyl dopa. Eumelanin contains little or no sulphur, in contrast to pheomelanin which contains approximately 10% sulphur.⁴⁻⁶ Various natural melanins are, however, neither pure eumelanin nor pure pheomelanin. They are copolymers of dopa and cysteinyl dopa. These have sulphur contents and other chemical and physical properties intermediate between pure eumelanin and pure pheomelanin.^{6,9-13}

Melanins contain stable free radicals, which can be detected by electron spin resonance (ESR). Both eumelanin and pheomelanin give one common ESR signal; but pheomelanin gives another ESR signal, which is not seen in the case of eumelanin. The above difference in the ESR signal is observed with melanins isolated from human black and red hair.^{11,14}

Certain other differences in the photochemical and photobiological properties of melanins from black hair and red hair have also been reported by us. Irradiation of the red hair melanin was found to produce considerable amounts of superoxide whereas irradiation of black hair melanin did not produce any detectable amounts of superoxide.¹⁵⁻¹⁷ Further, when Ehrlich ascites carcinoma cells were irradiated in the presence of red hair melanin there was a greater extent of cell lysis than when they were irradiated in the presence of black hair melanin.¹⁸

Our previous studies^{10,19,20} have shown that there are some qualitative differences in the physical and chemical properties of melanins isolated from human eyes having blue and brown irises (designated as blue and brown eyes respectively). These differences were observed in the oxidation properties of these melanins and the binding of some metabolites and drugs (e.g., protoporphyrin, chlorpromazine, and paraquat) to these melanins. The oxidation of reduced nicotinamide adenine dinucleotide (NADH) by the melanin-protoporphyrin complexes was also different for these two melanins from human eyes.

The present report is a part of our study on the comparison of the properties of the blue and brown eye melanins. In this investigation the photolytic

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effects of the two melanins were studied. For this purpose we used an *in-vitro* cell system. We have also compared the ESR signals of these melanins. Furthermore, we also investigated in the course of this study whether the various pigmented tissues of the eye, namely, iris, ciliary body, choroid, and retinal pigment epithelium, contain the same type of melanin or not.

Materials and methods

Human donor eyes having blue and brown irises were obtained from the Eye Bank of Canada (Ontario Division). The colour of the iris was coded by one person using a standard magnification and illumination.¹⁰ Only the eyes which had distinct blue and brown irises were selected. Eye donors were of both sexes and their ages ranged from 50 to 70 years. The average time between death and removal of the eyes was about six hours.

The eyes were dissected and the melanins were prepared from the iris, ciliary body, choroid, and retinal pigment epithelium according to the method previously described by us.¹⁰

The methods for the maintenance of Ehrlich ascites carcinoma cells in mice, the preparation of these cell suspensions, the labelling of the cells with ⁵¹Cr, and the determination of ⁵¹Cr release following cell lysis were carried out by the methods described previously.¹⁸

The cells were irradiated with a Westinghouse mercury vapor lamp. The cell suspensions were shaken in a waterbath at 37°C and irradiated by the UV light from the top. The lamp was placed at a height of 14 cm above the surface of the cell suspensions. The emission spectrum of the lamp and the irradiances with different filters were given in previous papers.^{6,17}

The formation of superoxide was determined by measuring the reduction of nitroblue tetrazolium chloride (NBT). The NBT reduction, which was inhibited by superoxide dismutase (SOD), was taken as a measure of the superoxide formation.¹⁷ Hydrogen peroxide (H₂O₂) was determined by the method of Wang and Nixon.²¹

The steps in the cell lysis experiments are summarised in Table 1.

The ESR measurements on melanins extracted from eye tissues were carried out with a Varian E-109 spectrometer operating at X-band (9.1 GHz) and employing 100 kHz field modulation. Measurements of magnetic field (H) and microwave frequency were made with a Radiopan MJ110-R gaussmeter and an EiP model 548 frequency counter respectively. The *g*-values were calculated to ± 0.0001 from $g = h/pH$, where *h* is Planck's constant and *B* is the Bohr

Table 1 Steps in the cell lysis experiments

1. Ehrlich ascites carcinoma was maintained in mice by serial transplantation.
2. The ascites fluid was withdrawn from the mice 7 to 10 days after the transplantation of the tumour.
3. The tumour cells were isolated and washed. The cells were suspended in medium 199 (Menon *et al.*).¹⁸
4. The cells were mixed with ⁵¹Cr and incubated.
5. The cells were sedimented, washed, and then suspended in medium 199.
6. The cells were either incubated in the dark or irradiated in the presence of melanin from the brown or blue eyes, or in the absence of melanin.
7. The cells were sedimented and the amount of ⁵¹Cr released in the supernatant was determined with a gamma counter.

Table 2 Release of ⁵¹Cr from labelled Ehrlich ascites carcinoma cells during incubation in the dark or irradiation in the presence of blue eye melanin (B1EM) or brown eye melanin (BrEM)

Reagents added*	⁵¹ Cr release (%) Mean $\pm$ SEM	
	Incubation	Irradiation
None	2.3 $\pm$ 0.5	1.0 $\pm$ 0.6
B1EM	2.5 $\pm$ 0.6	4.5 $\pm$ 0.6
BrEM	2.0 $\pm$ 0.4	2.7 $\pm$ 2.0

*Concentrations: B1EM and BrEM, 200 μ g/ml. The means $\pm$ SEM were calculated from the results of four experiments, done in duplicates.

magneton. Spectra were recorded on melanins previously incubated for 30 minutes in a solution of zinc sulphate (3 mM) at pH ca. 5. This procedure served to increase free radical concentrations and to accentuate any pheomelanin signals that were present.¹¹ Samples were maintained at -196°C in a Dewar flask inside the ESR cavity. For all ESR measurements the modulation amplitude was 4 G and the microwave power was 20 μ W.

Results

RELEASE OF THE ⁵¹CR

Ehrlich ascites carcinoma cells labelled with ⁵¹Cr were irradiated in the presence of blue or brown eye melanin. As a control the cells were either incubated in the dark in the presence of melanin or irradiated in the absence of melanin. The amount of ⁵¹Cr released under each of the above conditions was compared with the ⁵¹Cr released from the cells which were frozen and thawed.¹⁸ The results are given in Table 2. Cells which were incubated in the dark or irradiated in the presence of either the blue or brown eye melanin did not produce any greater ⁵¹Cr release than the control cells.

Reduction of NBT. Incubation or irradiation of

Table 3 Formation of hydrogen peroxide during incubation in the dark or irradiation of blue eye melanin (B1EM) or brown eye melanin (BrEM)

Reagents added*	H ₂ O ₂ formed (μ M) Mean $\pm$ SEM	
	Incubation	Irradiation
None	0.0	0.0
B1EM	0.7 $\pm$ 0.3	2.4 $\pm$ 0.2
BrEm	0.7 $\pm$ 0.3	3.3 $\pm$ 0.1

*Concentrations: B1EM and BrEM, 200 μ g/ml. The means $\pm$ SEM were calculated from the results of four experiments, done in duplicates.

Table 4 Magnetic parameters for eye melanins*

Sample	Line width, G [†]	g [‡]
Blue eye		
1, iris	5.50	2.0042
2, iris	5.50	2.0041
1, ciliary body	5.50	2.0040
2, ciliary body	5.50	2.0041
1, choroid	5.50	2.0043
2, choroid	5.50	2.0042
1, pigment epithelium	5.75	2.0042
2, pigment epithelium	5.75	2.0040
Brown eye		
1, iris	5.75	2.0041
2, iris	5.50	2.0041
1, ciliary body	5.50	2.0042
2, ciliary body	5.50	2.0043
1, choroid	5.50	2.0042
2, choroid	5.75	2.0042
1, pigment epithelium	5.50	2.0042
2, pigment epithelium	5.50	2.0041

*Measured in 3 mM zinc sulphate solution at pH 5. Temperature was -196°C .

[†] ± 0.25 G.

[‡] ± 0.0001 .

either blue or brown eye melanin did not show any reduction of NBT, indicating that no superoxide was formed under these conditions.

Formation of hydrogen peroxide. Incubation in the dark or irradiation of either blue or brown eye melanin showed the formation of only a small amount of H₂O₂ (Table 3).

ELECTRON SPIN RESONANCE

ESR spectra were obtained for melanins extracted from the iris, ciliary body, choroid, and retinal pigment epithelium of brown and blue eyes. Representative spectra are shown in Fig. 1. For each spectrum the magnetic parameters of line width and g value were measured as reported in Table 4. These spectral parameters (line width ca. 5.5 G, g ca. 2.004) were for the most part characteristic of eumelanins derived from dopa.²² In terms of the ESR spectroscopy melanins from the different individual eye tissues were almost indistinguishable.

Discussion

Our results showed that irradiation of blue or brown eye melanin did not produce any detectable amounts of superoxide, (as tested by the reduction of NBT). Irradiation of the carcinoma cells in the presence of blue or brown eye melanin did not produce any cell lysis. Our previous reports with hair melanins^{6, 11, 14-18, 23} showed that irradiation of pheomelanin produced considerable amounts of superoxide, whereas irradiation of eumelanin did not produce any superoxide under similar experimental conditions. Irradiation of Ehrlich ascites carcinoma cells in the presence of pheomelanin produced significantly more cell lysis than irradiation in the presence of eumelanin. Comparison of these findings with our present results indicates that the blue and brown eye melanins are essentially eumelanin. This is in conformity with our previous reports^{10, 19, 20} that these eye melanins had very low sulphur contents in contrast with the pheomelanins.

The ESR spectroscopy supports the conclusion that blue eye melanin and brown eye melanin are more like eumelanin than pheomelanin. The ESR signals further suggested that with respect to the quality of melanins, in the individual tissues from blue and brown eyes, namely the iris, ciliary body, choroid, and retinal pigment epithelium, these melanins did not differ.

Consideration of the present results and our previous results on the ocular melanins^{10, 19, 20} and

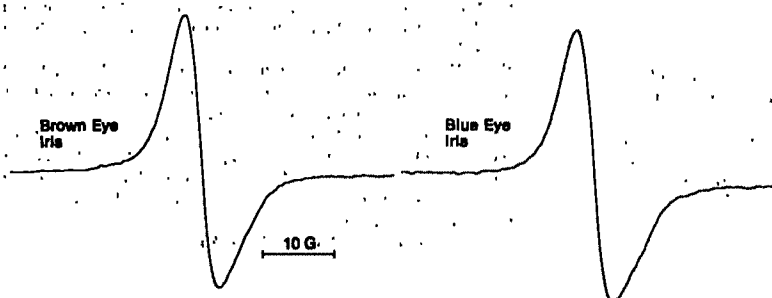


Fig. 1 ESR spectra of melanins extracted from brown eye iris (left) and blue eye iris (right). Spectra were recorded at -196°C on samples incubated in 3 mM zinc sulphate solution at pH 5.

non-ocular melanins^{6,11,14-18,23} lead to the possible conclusion that the classification of melanins into eumelanin and pheomelanin may be an oversimplification. It appears that there is a wide variety of melanins, two extreme prototypes of which may be represented by the melanins derived from dopa and cysteinyl-dopa. In between these extremes lie a number of melanins of a wide range of structures and properties. These intermediate melanins may be mixtures of pure eumelanin and pheomelanin, similar to dopa melanin and cysteinyl-dopa melanin, in diverse proportions or copolymers of dopa and cysteinyl-dopa.^{11,14} It is highly possible that in all cases several intermediates in the synthetic pathway get incorporated into the melanins. The wide spectrum of melanins differing in colours and probably in other properties may be explained better on the basis of the above concepts of the chemical structure of the melanins.

Our previous results confirm that both blue and brown eye melanins are essentially eumelanins. However, the melanins from these two sources are not exactly identical; certain distinct differences exist between them as has been reported before.^{10,19,20} From the information available at present these differences appear to be subtle when compared with the gross differences between the elemental composition and physicochemical properties of black and red hair melanins.^{6,11,14-18,23} The factors responsible for the differences in the oxidation properties of the blue and brown eye melanins and the binding of certain drugs to these melanins as reported earlier^{10,19,20} and the similarities in some of their other properties as reported in this paper are currently under investigation.

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A case of frosted branch angiitis

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SUMMARY We report a case of frosted branch angiitis in a 16-year-old-girl. She noted a sudden and severe visual disturbance in both eyes, without other systemic symptoms. Diffuse retinal oedema and unusual sheathing of retinal veins were characteristic in both fundi. Fluorescein angiography showed no occlusion of the sheathed retinal veins, but some paravenous extravasation of dye was found in the late phase. With high doses of systemic corticosteroids her fundi and visual acuity improved greatly, though the vessels continued to show severe narrowing. At three months the pattern visually evoked cortical potentials were found to be normal, while flash electroretinograms were absent. No systemic abnormality has been found to explain the aetiology of this condition.

In 1976 Ito *et al.*¹ reported a case of a 6-year-old boy who suffered from a bilateral acute uveitis with severe sheathing along all of the retinal vessels. They named this condition 'frosted branch angiitis'. Since this publication five similar cases have been reported in Japan, in Japanese.²⁻⁴ The disease occurs in children and has an acute onset with bilateral visual disturbance. It has been reported to respond well to steroid therapy. We report here the case of a girl who conformed quite well to the above description. The Correspondence to Yoshihiro Watanabe, MD, Department of Ophthalmology, School of Medicine, Chiba University, 1-8-1 Inohana, Chiba 280, Japan.

clinical features of previous cases of frosted branch angiitis are summarised and compared with those of similar retinal diseases.

Case report

A 16-year-old girl was first seen on 11 April 1985 with a one-day history of sudden redness and blurred vision in both eyes. Her visual acuity was counting fingers at 50 cm in both eyes. Ciliary injection and a cellular reaction was seen in the anterior chamber. The intraocular pressures were within normal limits. The

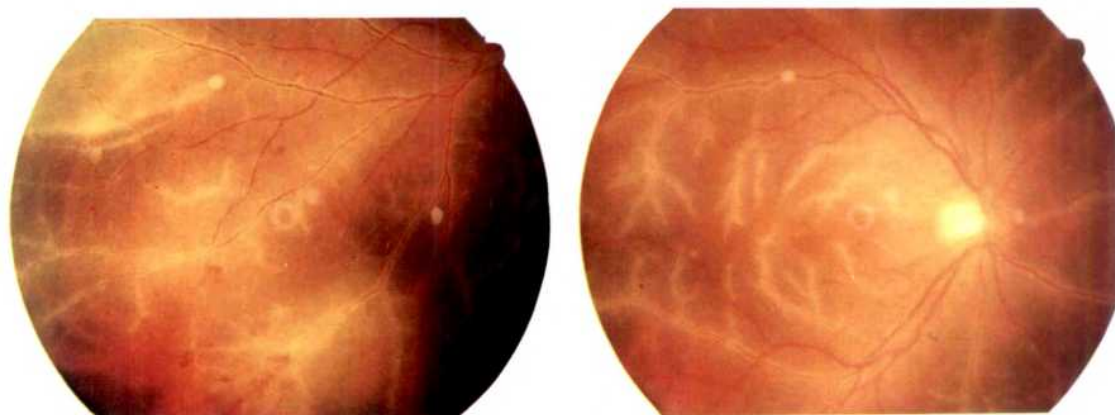
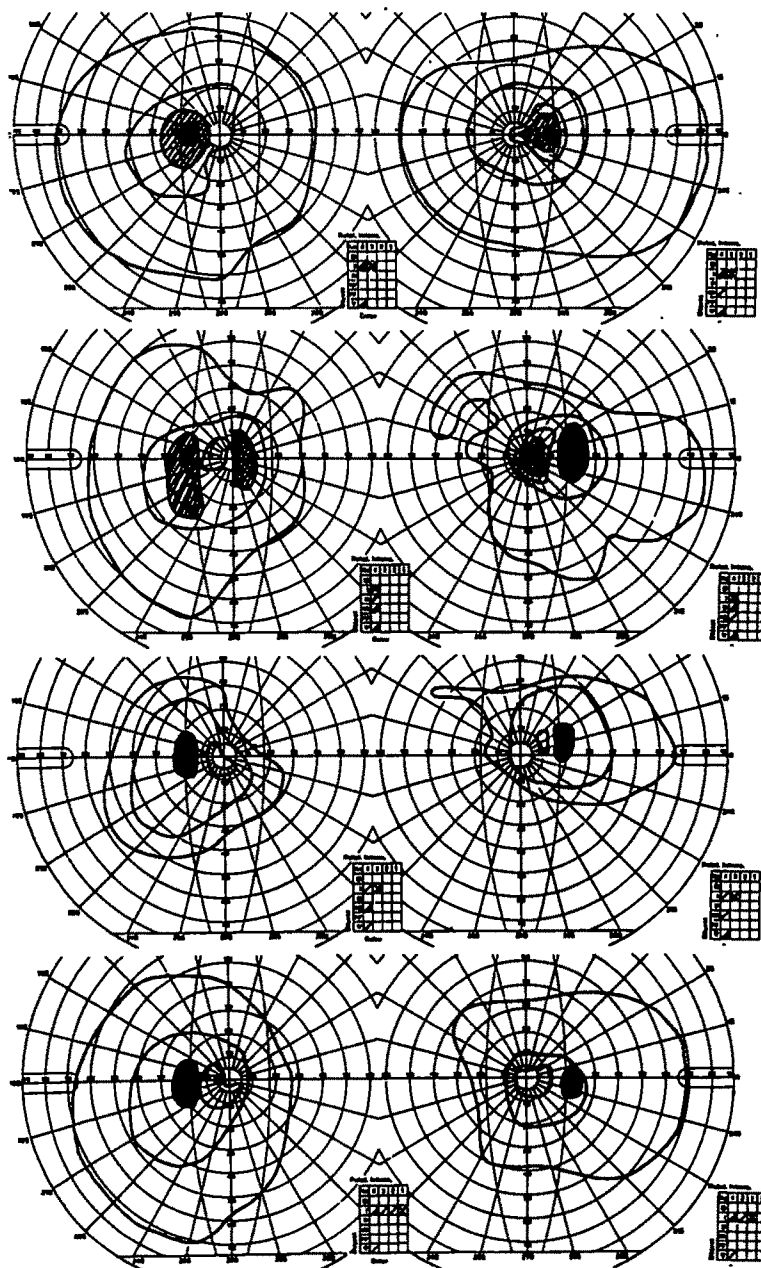


Fig. 1 Right eye, 11 April 1985. Left, temporal periphery. Severe sheathing of the veins and some blot haemorrhages adjacent to veins. Right, posterior pole. Diffuse retinal oedema and severe sheathing of the veins are seen, but the optic disc is almost normal.

Fig. 2 Change of visual fields.
 Top row, 11 April 1985. Second
 row, 17 April 1985. Third row,
 28 April 1985. Fourth row, 10 June
 1985.



vitreous was slightly hazy and the retina was oedematous, with scattered nerve fibre haemorrhages. Severe sheathing along all the veins was found throughout the retina in both eyes except in areas surrounding the optic discs; the sheathing was more severe peripherally (Fig. 1). Dilatation or tortuosity of the veins was not seen. The optic discs were almost normal.

A visual field test showed bilateral enlargement of

the blind spot and general deterioration of sensitivity (Fig. 2).

Fundus fluorescein angiography demonstrated that the retinal veins were patent, but extravasation and staining of veins were obvious in the late stages (Fig. 3). Because the patient complained of dizziness and malaise after the injection of fluorescein, fundus angiography was not repeated.

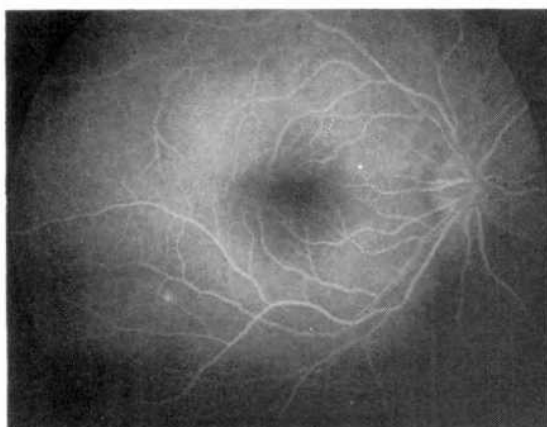


Fig. 3 Right eye, 12 April 1985. Fluorescein angiogram. Left, early phase. No abnormalities are found. Right, photomontage, late phase. Vessels round the macula stain with fluorescein, and extensive dye leakage from veins is seen in the periphery.



No systemic abnormality was found. Red and white cell counts, haemoglobin, plasma proteins, urea, and electrolytes were normal. Chest x-rays were also normal. There was no serological evidence of syphilis, toxoplasmosis, or rheumatoid arthritis. A skin test for tuberculosis was negative. Serum complement levels for herpes simplex virus, herpes zoster virus, and cytomegalovirus were within normal limits.

CLINICAL COURSE

The patient was admitted to hospital immediately,

and treatment was started with topical cycloplegics and 0.1% betamethasone, and with systemic betamethasone (3 mg/day). This treatment was continued for three consecutive days, but there was no improvement, and the visual acuity fell to counting fingers at 30 cm in both eyes. On the fourth day the patient was therefore switched to 20 mg/day of dexamethasone (Fig. 4). The retinal oedema, sheathing along the veins, and cellular floaters in the anterior chamber improved by the next day. The sheathing almost disappeared on the 10th day, but sheathed veins and adjacent retinal haemorrhages remained in the peripheral areas, and hard exudates similar to the macular star figure were seen in both posterior poles. At this stage irregularities in calibre of the veins and narrowing of the arteries appeared (Fig. 5).

After 20 days of treatment the cells in the anterior chamber had almost disappeared and the visual acuity

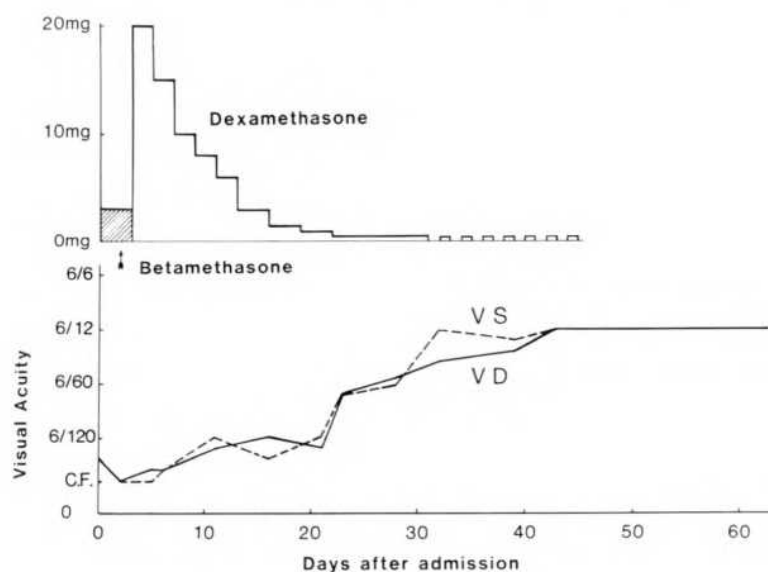


Fig. 4 Steroid therapy and time course of visual acuity.

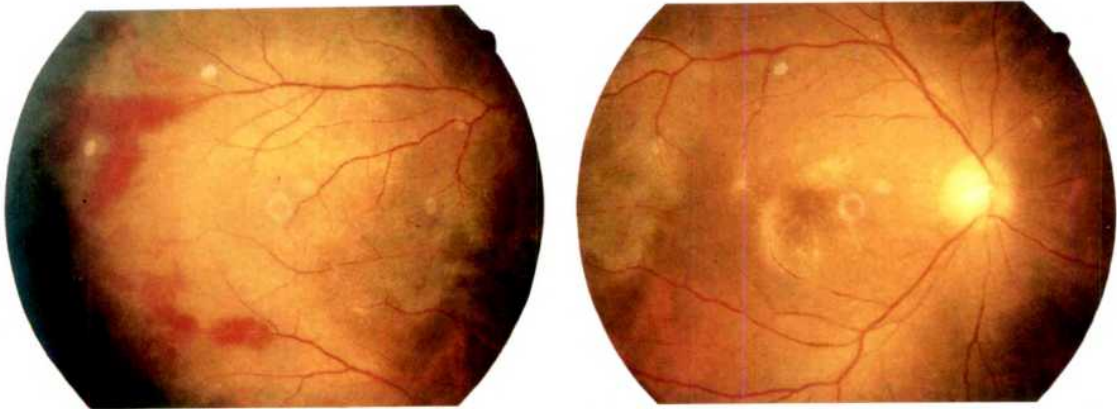


Fig. 5 Right eye, 22 April 1985. Left, temporal periphery. Diffuse hard exudates and haemorrhages along the veins. Arteries are very narrow. Right, posterior pole. Hard exudates like a macular star figure are seen.

had slightly improved (Fig. 4). By the 40th day her acuity had improved to 6/12 in both eyes, but attenuation of retinal veins continued to be seen. She was discharged on the 41st day. Dexamethasone was reduced gradually and completed on the 45th day. The total dosage of dexamethasone was 141.5 mg.

Three months after the patient's initial presentation faint hard exudates in the macular areas and abnormal reflexes around the maculae were still present. In the mid and far periphery the vessels were so narrow that they were difficult to recognise, and even in the posterior pole the arteries were severely attenuated. Some blot haemorrhages were present in the mid periphery. Coalescence of small, sharply demarcated, atrophic lesions was seen in the far peripheral areas, especially in the temporal periphery (Fig. 6). Her visual acuity improved to 6/9 five months after onset.

CHANGES OF VISUAL FIELDS

The bilateral central scotoma that appeared six days after initial presentation disappeared in about two weeks. However, generalised constriction of visual fields progressed. Her visual field then enlarged slowly, but the improvement almost stopped near the end of the second month after initial presentation. The patient was left with a general constriction and slight deterioration of central sensitivity. Visual field constriction was more severe on the nasal side, which corresponded well with the atrophic appearance of the temporal peripheral retina.

ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL TESTING

Almost no electroretinogram (ERG) response could be elicited on the fifth day after the patient's initial presentation. Only a slight recovery of the response

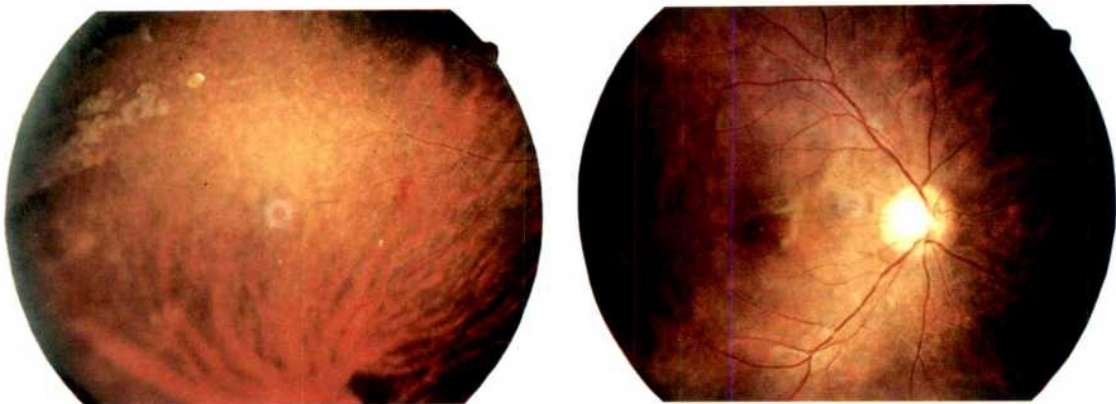


Fig. 6 Right eye, 22 July 1985. Left, temporal periphery. Sharply demarcated atrophic lesions and narrowing of vessels like threads. Right, posterior pole. Hard exudates have almost disappeared. Narrowing of vessels, particularly arteries, is seen.

was found on the 54th day, and no further improvement was observed even on about the 100th day. On the other hand pattern visually evoked cortical potentials (pattern VECPs) using check size of 18.9 minutes, contrast of 80%, reversing at a rate of 3 or 10 per second, performed three months after onset were normal both in peak latencies and in amplitudes (Fig. 7). Colour vision of both eyes was normal with the Ishihara test plates and Farnsworth panel D-15, but the left eye showed a mild red-green deficiency with standard pseudoisochromatic plates.

Discussion

The main features of frosted branch angiitis as originally reported by Ito *et al.*¹ can be summarised as follows: (1) bilateral acute visual disturbance in a healthy child. (2) The whole retina is swollen and there

is severe sheathing of the retinal vessels, so that they look like frosted branches of a tree, especially at the periphery. (3) Fundus fluorescein angiography shows almost a normal pattern in the first stage, but leakage of the dye from vessels is seen in later stages; in particular, the sheathed vessels show no sign of occlusion or stasis. (4) Visual fields show a marked concentric constriction during the acute stages of the disease but improve with the reduction of the swelling and inflammation. (5) ERGs are markedly abnormal. (6) No systemic abnormality is found. (7) High doses of systemic corticosteroids are effective in treating the disorder, and the visual acuity recovers to almost a normal level. (8) The disease has not recurred.

The features of the other cases of frosted branch angiitis previously reported are summarised in Table 1.

In all cases both eyes were affected, and the visual acuity fell rapidly within a week to less than 6/30.

The fundus findings in these cases were similar and can be summarised as follows: (1) The optic discs were almost always normal, though slight oedema or hyperaemia was seen in some cases. (2) In the acute stage the whole retina was oedematous and opacified. Intense sheathing of retinal vessels, especially veins, was seen throughout the fundi, but was severer in the peripheral areas, showing the appearance of frosted branches of a tree. These inflammatory changes gradually became normal by absorption of retinal oedema and improvement in the sheathing. (3) Geographic atrophic lesions remained at the periphery in most cases. Hard exudates were often seen in the maculae or elsewhere during the absorption of the retinal oedema.

In the present case intense narrowing of vessels remained after subsidence of inflammation in addition to the above mentioned peripheral atrophic lesions. As the retinae were atrophied by the severe inflammation, it is doubtful whether the vascular narrowing will return to normal.

From the above summary of reported cases, including ours, the pathological condition of frosted branch angiitis can be defined as follows. It is an acute panuveitis with severe vasculitis that occurs in the whole retina. Sakanishi *et al.*² suggested that the atrophic lesions that remained at the periphery are a consequence of poor blood perfusion of the peripheral retina. The peripheral areas are therefore more susceptible to damage. The present patient had briefly a central scotoma similar to optic neuritis, but the cause is likely to be macular oedema rather than direct damage to the optic nerve. This explanation is supported by the exudates that appeared later in the macular area. Diminished ERGs recorded three months after onset suggest that substantial damage occurred to the retina as a whole. The normal pattern

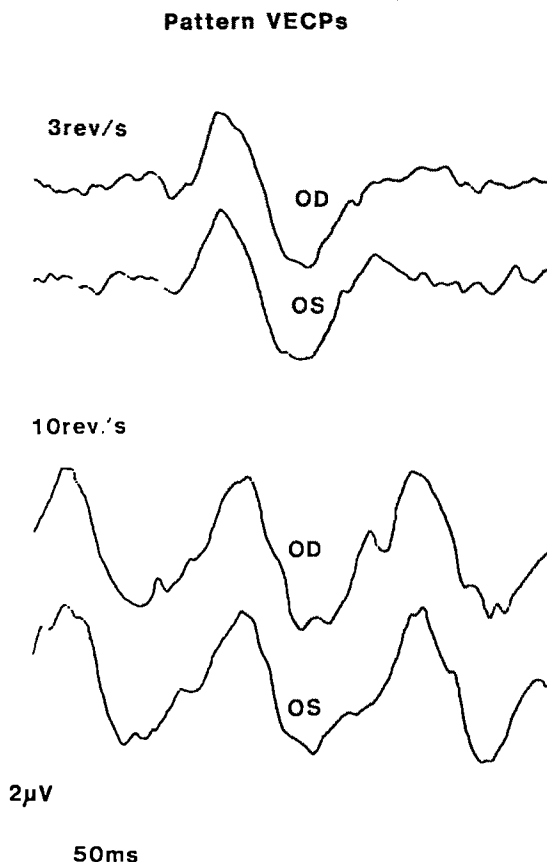


Fig. 7 Pattern VECPs recorded three months after onset. The peak latency of P100 component of transient responses (Top) is normal and the amplitude is not reduced both in transient and steady state responses (bottom). (Stimulus field 8×10 degrees, check size 18.9 minutes, contrast ratio 80%, 128 pattern reversals.)

Table 1 Cases of frosted branch angiitis

Authors	Year	Age	sex	Worst VA		Final VA		Worst VF	Final VF
				Right	Left	Right	Left		
Ito <i>et al.</i> ¹	1976	6	M	6/120	6/60	6/6	6/5	Concentric defect	Normal
Sakanishi <i>et al.</i> ²	1984	9	F	CF	6/120	6/5	6/5	Not described	
		8	M	6/60	6/30	6/9	6/6	Not described	
Yamane <i>et al.</i> ³	1985	9	F	CF	CF	6/5	6/5	Not described	
Higuchi <i>et al.</i> ⁴	1985	9	F	LP	LP	6/12	6/7	Not described	
Watanabe <i>et al.</i>	1986	16	F	CF	CF	6/9	6/9	Concentric defect	Generalised constriction
								Central scotoma	

VA = visual acuity. VF = visual field. CF = counting fingers. LP = light perception.

VECPs found at the same time, however, indicate that the visual pathway from macula to occipital lobe returned to a normal condition.

No aetiological abnormality has yet been identified. However, systemic steroid was reported to be effective. Although the natural course of frosted branch angiitis is unknown, anti-inflammatory drugs are essential to minimise retinal inflammatory damage.

The differential diagnosis includes four diseases with sheathing of retinal vessels:

(1) Acute retinal necrosis⁵ (Kirisawa type uveitis and bilateral acute retinal necrosis^{6,7}). Sheathing is also seen, but is mainly restricted to arteries. Fluorescein angiography shows occlusion of arteries and capillary beds. This disease may occur monocularly, and in bilateral cases the day of onset in each eye is usually different. In addition children are rarely affected. The prognosis is extremely poor in contrast to that of frosted branch angiitis.

(2) Peripheral uveitis.⁸ This disease has been considered to be not a single entity but a syndrome from various causes. Though sheathing of veins may be seen in peripheral areas, subjective signs are commonly mild.

(3) Retinitis caused by cytomegalovirus or herpes simplex virus.⁹⁻¹² These viral infections tend to affect patients who are immunosuppressed. Pathological changes of the fundus are not so diffuse as in frosted branch angiitis. Titres against these viruses have always been negative in frosted branch angiitis.

(4) Eales' disease.¹³ Although vessels may be sheathed in peripheral areas, fluorescein angiography shows obliteration of retinal capillaries and vessels.

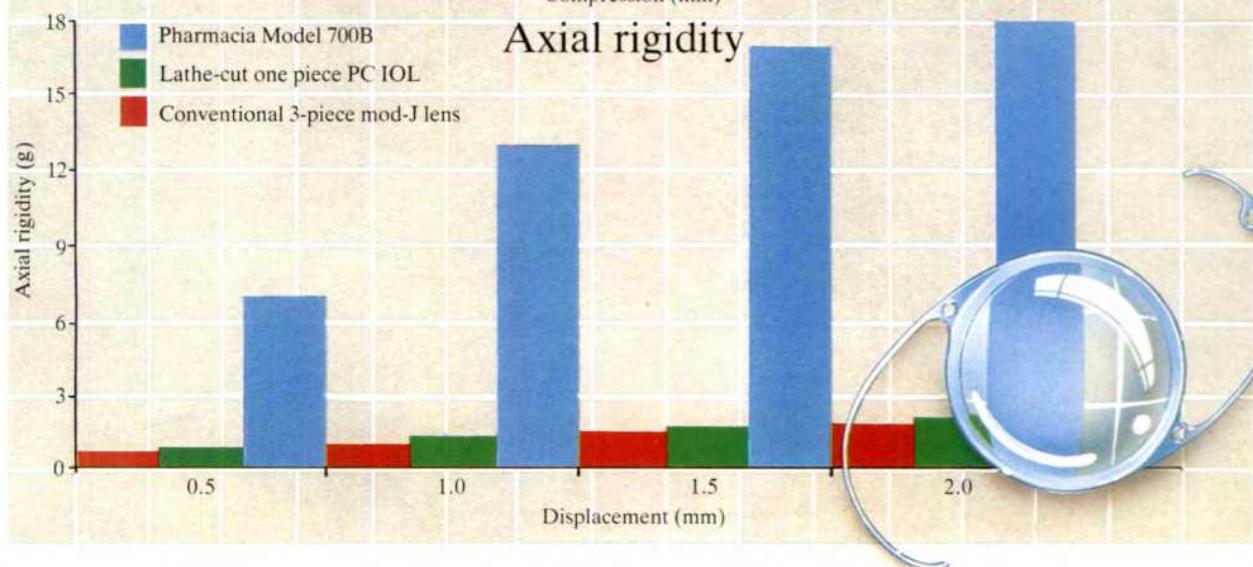
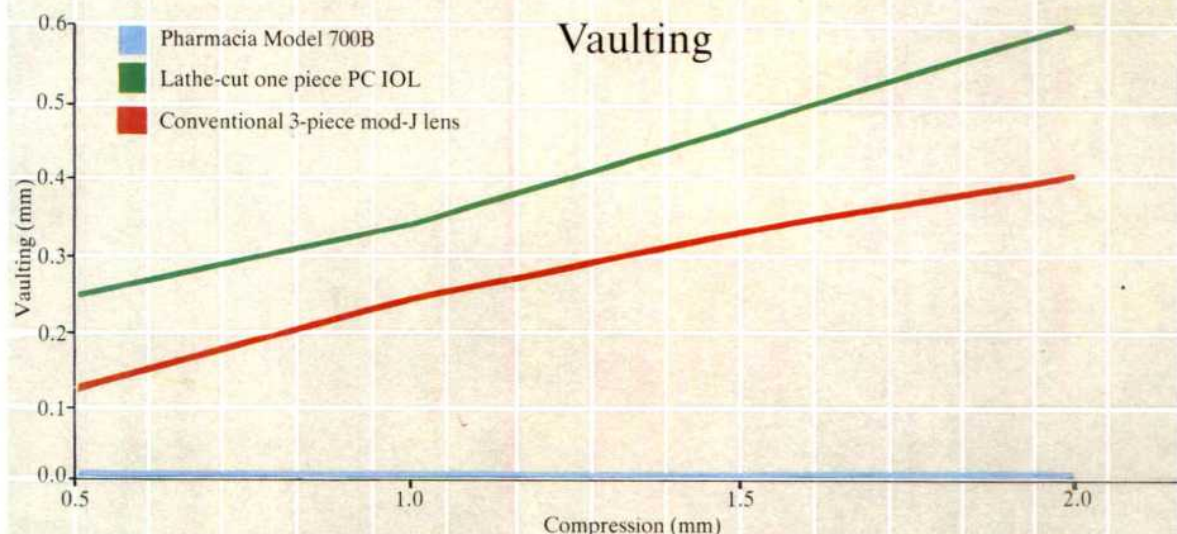
Central visual acuity is retained unless vitreous haemorrhages cover the posterior pole.

Frosted branch angiitis seems to be a newly recognised disease, and further studies will be necessary to understand its causation.

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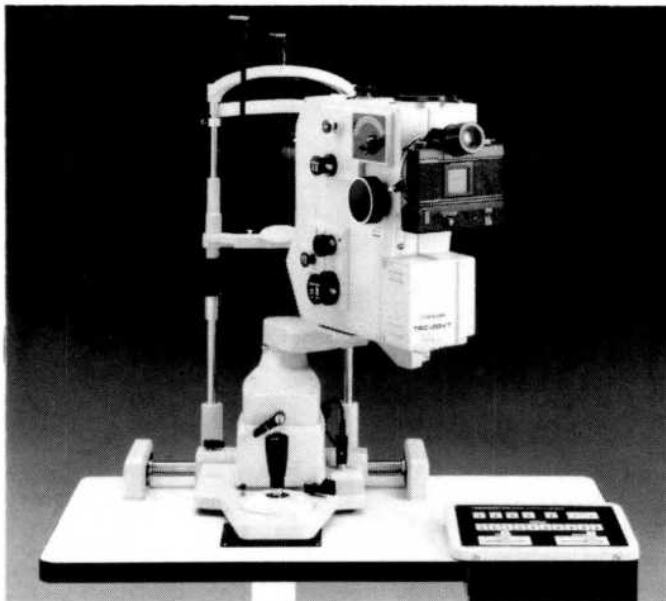
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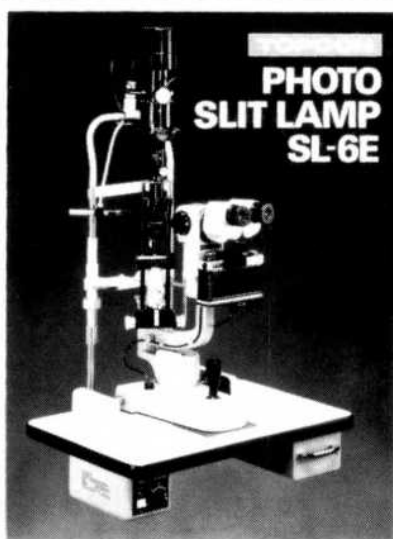
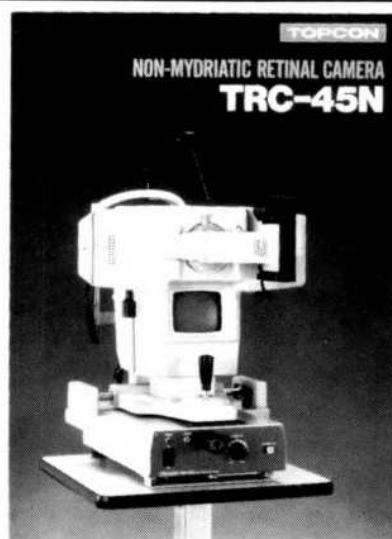


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'Rush' type retinopathy of prematurity: report of three cases

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SUMMARY Three premature infants observed to develop severe stage III retinopathy of prematurity (ROP) at 3 to 5 weeks of age received immediate treatment by cryoablation and photocoagulation, with good results. The critical importance of the ophthalmic examination of premature babies from the age of 2 weeks, so as not to overlook such cases of 'rush' type ROP is stressed and the difficulty involved in treating such small neonates is discussed.

In the great majority of premature babies with retinopathy of prematurity (ROP) the disease develops gradually and relatively slowly. The early stages of ROP usually appear six to eight weeks after birth.^{1,3} Therefore the Committee on Fetus and Newborn of the American Academy of Pediatrics¹ and Palmer^{2,3} recommended that the eyes of premature infants should be examined on discharge from the nursery or at the age of 7 to 9 weeks. Reports in the Japanese literature, however, indicate that ROP may also take a more rapid course within the first month of life.^{4,6} These investigators found that at the age of 3 to 5 weeks the disease present in zone I or II rapidly progressed to severe ROP (stage III according to the new international classification⁷) and they termed this 'rush' type ROP, concluding that the prognosis for vision was very poor.

We describe here three infants with 'rush' type ROP in whom treatment by cryoablation and photocoagulation yielded good results.

Case reports

CASE 1

A female infant was born in the 26th week of gestation with a birth weight of 950 g. The apgar score was 6 at birth and 8 five minutes later. Assisted ventilation was immediately started with 100% oxygen and continued for three weeks with FiO₂ (fraction inspiratory oxygen) 25%. The Po₂ was maintained at 50-70 mmHg, but there were three short episodes of Po₂ above 100 mmHg. The first eye

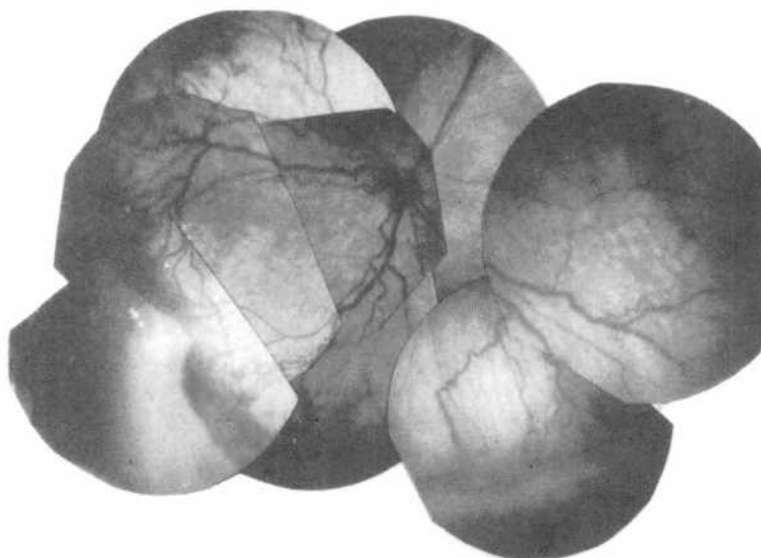
examination made at the age of two weeks disclosed remnants of tunica vasculosa lentis and a hazy vitreous in both eyes. The fundus examination revealed the presence of retinal vessels in zone 1. The angle between the large vessels was 120°. At the age of 3 weeks congestion of posterior pole vessels and the beginning of fibrovascular proliferation (FVP) were found. At 4 weeks there was severe congestion of the iris vessels with rigidity of the pupils, and the fundus examination showed 360° of severe stage III ROP. Both eyes showed similar retinal changes (Figs. 1,2) and the angle between the large vessels was 100°.

Under general anaesthesia a conjunctival incision 3-4 mm in length was made in each quadrant. After undermining with blunt-ended scissors, a cataract cryoprobe was inserted into each of the incisions well behind the equator, and cryotherapy of the avascular retina was performed through 360°. Particular care was taken to defrost the probe before moving it to another location. Because the inferior oblique muscles interfered with the cryopexy probe owing to the posterior location of the disease, the avascular retina close to the macula was photocoagulated with xenon light. Twenty-four hours after this procedure the iris vessels were less engorged and the pupils were less rigid. The FVP started to disappear, and three weeks later progression of the retinal blood vessels between the cryopexy scars was observed (Figs. 3 and 4). The angle between the large vessels was 70°, but the macula was not displaced.

Three months later the eyes appeared to be orthophoric with central fixation, and there was no nystagmus. The anterior segments were normal, and

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Fig. 1 • Fundus photograph of the right eye of case 1 (at 30 weeks of gestation) showing the posterior pole with congested vessels in zone I only and extensive fibrovascular proliferation through 360° at the edge of the advancing vasculature (severe ROP, stage III).



fundus examination revealed cicatricial changes following peripheral retinal ablation (stage II according to the classification of Reese *et al.*⁸ On retinoscopy a +1.0 hypermetropia was found in both eyes.

CASE 2

This infant was born at 26 weeks of gestation with a birth weight of 800 g. The apgar score was 6 at birth and 7 after five minutes. Assisted ventilation was started because of respiratory distress. PO_2 range

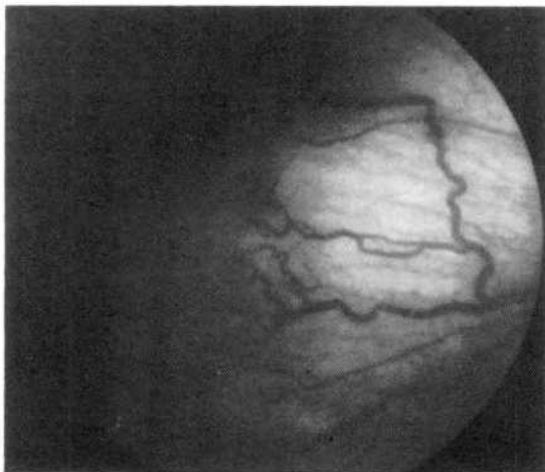


Fig. 2 Fundus photograph of the right eye of case 1 (30 weeks gestational age) showing the progression of the congested vessels in association with florid fibrovascular proliferation near the advancing vascular border (severe ROP, stage III).

was 50 to 70 mmHg. Oxygen treatment was given for 10 days. At the age of 2 weeks examination revealed normal anterior segments in both eyes and remnants of tunica vasculosa lentis. Fundus examination showed retinal vessels only in zone I in both eyes. At the age of 4 weeks there were pupillary rigidity and engorgement of the iris vessels, with active stage III of severe ROP in zone I–II, 360°. On the same day cryotherapy was carried out on the avascular retina anterior to the fibrovascular proliferation. The procedure was performed under local anaesthesia achieved with drops of a local anaesthetic and four injections of lignocaine 2% into the subtenon space. Four conjunctival incisions at the limbus enabled the cataract cryoprobe to reach the entire avascular retina, so that xenon photocoagulation was not necessary.

Two weeks later disappearance of the pupillary rigidity as well as regression of the large retinal vessels congestion and the FVP were observed. At the age of 2 months fundus examination showed normal posterior poles and progression of the retinal vessels between the cryoscars in the equator, with cicatricial stage I. No nystagmus was observed, and the child has had a good fixation in both eyes.

CASE 3

This female infant was born at 26 weeks of gestation weighing 870 g. The apgar score was 2 at birth and 5 after five minutes. Assisted ventilation with 100% O_2 was started because of left lung hypoventilation and atelectasis of the upper lobe of the right lung, with recurrent episodes of apnoea. PO_2 was in the range of 70 mmHg. Oxygen was given for 12 days. Eye

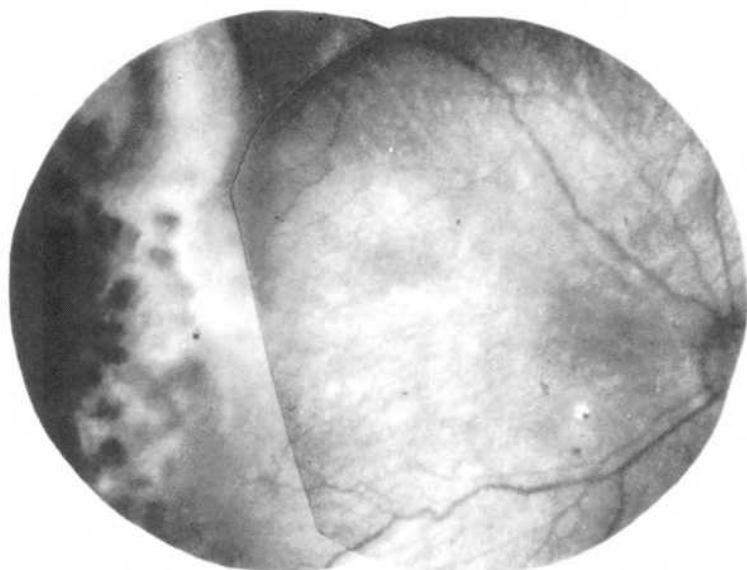


Fig. 3 Fundus photograph of the right eye of same case at the age of 3 months following photocoagulation combined with cryotherapy. Photocoagulation and cryotherapy scars are seen temporal to the macula (bottom).

examination performed at the age of 2 weeks revealed remnants of tunica vasculosa lentis with normal anterior segments. The fundus examination showed extension of the retinal vessels to zone I. Two weeks later congestion of posterior retinal vessels was observed, and one week later, at the age of 5 weeks, severe active ROP (stage III) was found in zone I-II, 360°. On the same day cryotherapy was performed on the avascular retina, 360°, with local anaesthesia, achieved as described for case 2. One week later the congestion of retinal vessels had lessened and there was some regression of the FVP. Three weeks later the FVP had disappeared. At the age of 3 months the angle between the large vessels

was 100° with some dragging on the macula. Progression of the retinal vessels between the cryoscars and towards the equator through 360° was observed. The retinal changes were those of cicatricial stage II.

Discussion

The rush type ROP described in the Japanese literature¹⁶ appears to occur only in premature babies of extremely low birth weight. The fibro-vascular proliferative changes involve the entire circumference of the posterior retina. On the temporal side the retinal vessels reach the lateral border of the macula, and on the nasal side they run tortuously only 2-3 disc diameters from the optic nerve head. These changes appear in zone I or II of the new international classification of ROP.⁷ In most cases retinal detachment was found to develop within a very short period from the onset of the retinopathic changes.

The increased chance for survival of neonates of extremely low birth weight in critical general condition creates a much larger population at risk to develop the severe stages of ROP and also rush type ROP. In our hospital the three infants presented above constitute 5% of the 50 cases of ROP requiring cryoablation treatment during recent years.⁹

There can thus be little doubt that it would be advisable to institute routine examination of all premature infants, weighing less than 1000 g and born at the age of 28 weeks or less, as early as two weeks after birth. We are of the opinion that this procedure is harmless, as it is performed in the nursery intensive care unit while the baby is in the



Fig. 4 Fundus photograph of the right eye of same case at the age of 3 months showing cryotherapy scars nasal to the disc, and retinal vessels progressing between the scars.

incubator, in which body temperature, respiration, and all the vital signs are well controlled. When the first examination is made only at the age of 7 to 9 weeks, initial retinal changes are apt to be missed, and in these eyes there may already be retinal detachment or severe cicatricial changes which will compromise the infant's vision.

Therefore, when rush type ROP is diagnosed immediate treatment is indicated. Although controlled clinical trials and long term results are still lacking, there is increasing evidence to show that cryotherapy or photocoagulation, or a combination of the two, are beneficial in treating active stage III ROP.^{4,6,9-13} Circumferential ablation of the avascular peripheral retina, while getting as close to the advancing edge of the retinal vasculature as possible, has been shown to achieve retinal quiescence within hours.⁹ We believe that when the disease exists in zone I a combination of cryotherapy and photocoagulation is necessary to arrest it. This can be done only under general anaesthesia or with local subtenon injection. When signs of the disease are found in zone II, cryotherapy alone should suffice, and this is performed with local anaesthetic drops or four-quadrant injection of lignocaine.

An important point is the difficulty involved in the treatment of such small babies having a weight of less than 1000 g who require oxygen and whose general condition is unstable. For this reason a neonatologist should attend throughout the procedure. Furthermore, to prevent occlusion of the central retinal artery¹⁴ particular care must be taken not to press too vigorously on the eye during cryoapplication and also to observe continuously the central artery even while the cryoprobe is being defrosted.

In conclusion, we should like to stress again the critical importance of ophthalmic examination in premature infants from the age of 2 weeks, with

immediate initiation of treatment when stage III ROP is diagnosed.

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Correspondence

Foveomacular retinitis

SIR, Kuming's description¹ from South Africa of 10 cases of foveomacular retinitis as an entity distinct from solar retinopathy rekindles old controversies.^{2,3} A knowledge of the racial origin of their patients would be helpful, as a predominance of low pigmentation has been noted in other series.^{4,5} In view of more recent reports,^{6,8} including one example from our own series,⁹ indicating that sunbathing without direct sungazing may provoke this retinal lesion, there would appear to be only one aetiology.

Regarding the nature of the phototoxic macular lesion, I feel that a good clinicopathological correlation is achieved with recourse to experimental work.^{10,11} The essential finding is that of pigment epithelial depigmentation associated with filamentary proliferation giving rise to a feature designated as a fibrillar 'tuft' in our own report.⁹

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N A JACOBS

The statement that recent reports indicate that sunbathing without direct sungazing may provoke this retinal lesion is not accurate. Ridgway's report documents a patient who gazed at the sun while sunbathing. MacFaul documents only those cases who sustained a macula injury following direct gaze at an eclipse in 1966, except for case 19 who while sunbathing gazed directly at the sun for up to six minutes, and Gladstone's cases all admitted looking at the sun while sunbathing.

Thus one must disagree with the statement that there appears to be only one aetiology, as all the references quoted show that the patients concerned looked directly at the sun. The evidence quoted only confirms that direct sungazing is dangerous and to be avoided at all costs. None of my patients admitted sungazing, in fact all strongly denied this. In none of my patients was there a specific time of onset that could be related to any form of sunbathing or sun exposure.

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BS KUMING

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SIR, All the patients described in my paper were Caucasian. While agreeing that the aetiology is controversial, the fact still remains that my patients (and many others) flatly deny any direct gazing at the sun. Nowhere in the paper by Jacobs *et al* do they state that their one patient who sunbathed did not have direct exposure to the sun. It is not unlikely that their patient inadvertently opened his eyes while sunbathing, as did these patients described by Gladstone and Tasman.

The levels of sunshine in South Africa are far higher than that in the UK. Many thousands of patients take to the beaches to sunbathe throughout the year, yet the reported incidence of solar retinopathy in SA after sunbathing is practically nil.

Lenses for fundus examination

SIR, Many ophthalmologists in training, especially in the junior grades, are faced with significant expense when acquiring all the necessary tools of the trade. It may be of interest to know that there are alternative sources for some of these items, in particular the lenses used for fundus examination by the indirect method, using either the indirect ophthalmoscope or the slit-lamp microscope.

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90-dioptre aspheric lenses are extremely useful for examining the optic disc and macula, without the need for a contact lens, while the patient is sitting at the slit-lamp. Small lenses of approximately the same power are available



Fig. 1 Stand with legs removed.

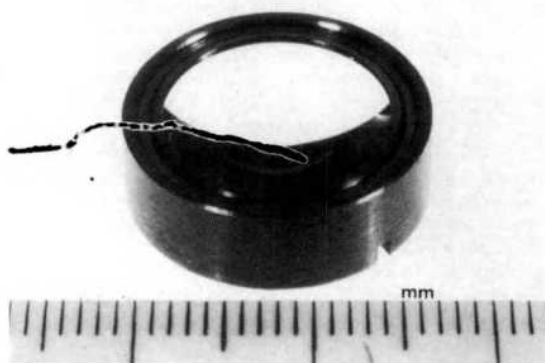


Fig. 2 Non-spheric lens of approximately 90 dioptres.

from optical equipment suppliers for a few pounds (Fig. 2). They are not aspheric and so tend to distort the image somewhat, but in my experience this distortion is not significant.

RAYMOND BROWN

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Book reviews

The Eye in General Practice. By C R S Jackson and R D Finlay. Pp. 145. £12.00. Churchill Livingstone: Edinburgh. 1985.

This book is a very able revision and restyling of an old and successful favourite. It is strongly recommended, especially to young doctors wishing that they had spent more time on ophthalmology as an undergraduate and now facing difficult and crucial decisions. It will also interest older general practitioners having learnt the hard way, now realising the many advances in ophthalmology in recent years and wishing to know more about them.

ROLIVER

Goldberg's Genetic and Metabolic Eye Disease. 2nd Edn. Edited by William Andrew Renie. Pp. 574. £72.90. Churchill Livingstone: Edinburgh. 1986.

Textbooks on genetic eye disease are always most welcome, and this second edition of Goldberg's book is no exception. I read it with both pleasure and some frustration. The first seven chapters, on methods of study in genetic eye disease, provide an excellent introduction to modern applied human genetics and can be recommended to all who wish to understand the 'new genetics'. The remainder of the book is concerned with the genetic determination of clinical eye disease and includes several excellent chapters, as well as the frustrating omission of several important genetically

determined eye diseases which preclude this being as useful a 'bench book' for the practising ophthalmologist as it could be. It can, however, be recommended to all with an interest in paediatric ophthalmology and genetic eye disease, and particularly to ophthalmologists in training.

BARRIE JAY

Notes

Australia Cranio-Maxillo-Facial Foundation

The Australian Cranio-Maxillo-Facial Foundation will be holding an International Workshop on cranio-facial trauma in Adelaide, South Australia, on 9-14 October 1988. Details from Mrs D Moody, Executive Officer, 226 Melbourne Street, North Adelaide S A 5006, Australia.

Corneal graft failure

The 4th Dermot Pierse lecture will be given by Professor DJ Coster (Adelaide, Australia) in the Barnes Hall, Royal Society of Medicine, on 23 September 1987. Its title will be 'The mechanism of corneal graft failure.' The lecture will start at 1845 h and will be preceded by wine and canapés from 1800 h. Further information obtainable from Dr H Jonathan Kersley, 80 Harley Street, London W1N 1AE.

Retinitis pigmentosa

The Fifth International Retinitis Pigmentosa Congress will be held at the Hyatt-Regency Hotel in Melbourne, Australia, on 4-7 November 1988. It will follow the Annual Meeting of the Royal Australian College of Ophthalmology on 29 October-4 November 1988. Details from the Conference Secretary, 46A Oxley Road, Hawthorn 3122, Victoria, Australia.

Plastic surgery

A postgraduate course on Ophthalmic, Plastic, and Reconstructive Surgery - Past, Present, and Future, will be held on 10-11 December 1987 at the Hyatt on Union Square Hotel, San Francisco, USA. Details from Extended Programs in Medical Education, University of California School of Medicine, San Francisco, CA 94143, USA.

European meeting

The 18th European Ophthalmology Meeting will be held by the European Contact Lens Society of Ophthalmologists and the Belgian Society of Contact Lenses and Intraocular Implants at Brussels on 16-18 September 1988. Details from Dr Kelman Wisnia, General Secretary Sobeveco, Avenue Jeanne 19A, Box 16, 1050 Brussels, Belgium.

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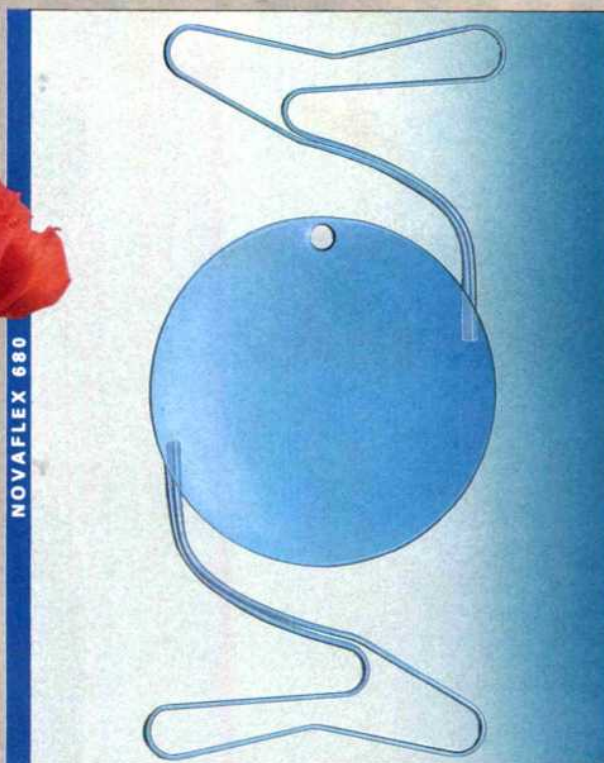
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Ophthalmic findings in a group of ambulatory patients infected by human immunodeficiency virus (HIV): a prospective study

R C HUMPHRY,¹ J N WEBER,² AND R J MARSH¹

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SUMMARY Twenty-eight patients with either the acquired immune deficiency syndrome (AIDS) or persistent generalised lymphadenopathy (PGL) were studied prospectively as outpatients for up to one year. Six patients had fundal cotton wool spots at some stage of their follow-up and all six suffered opportunistic infections associated with AIDS. We suggest that ocular abnormalities may be prognostic for opportunistic infection in AIDS and discuss the wide range of ophthalmic complications consequent to HIV infection.

The human immunodeficiency virus type III (HIV) is now implicated as the cause of the acquired immune deficiency syndrome (AIDS) and of related disorders, such as persistent generalised lymphadenopathy (PGL).¹⁻⁵ A recent study of AIDS and AIDS risk patients by both membrane immunofluorescence and competitive radioimmunoassay showed that 97% of AIDS patients were seropositive for antibodies to HIV, as were 89% of patients with PGL, 17% of symptomless homosexual men, 34% of haemophiliacs receiving pooled clotting factors, and 1.5% of intravenous drug abusers. None of more than 1000 unselected blood donors were seropositive.⁶

AIDS is a severe disorder of immunoregulation found in previously healthy subjects and occurs most commonly in homosexual males, bisexuals, haemophiliacs, and intravenous drug abusers.⁷⁻⁹ Patients may develop opportunistic infections, Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and a form of presenile dementia due to HIV related encephalopathy.¹⁰ The ocular features of AIDS have been reported as including retinal lesions such as cotton wool spots, intraretinal haemorrhages, and toxoplasma and cytomegalovirus (CMV) retinitis, together with conjunctival Kaposi's sarcoma and multiple cranial nerve palsies.¹¹⁻¹⁴ Although these reports do not suggest that cotton wool spots repre-

sent a prognostic 'marker', severe CMV retinitis occurs in the more severely immunocompromised patients, and an ocular motility disorder suggests an infectious or neoplastic encephalomeningitis.¹⁵ No prospective study has assessed the temporal associations or prognosis of independent ocular disease—that is, the ophthalmic features of HIV disease rather than manifestations of AIDS.

Persistent generalised lymphadenopathy (PGL) is an AIDS-related complex (ARC) and is a syndrome found in a similar epidemiological group as for AIDS. It is clinically characterised by lymphadenopathy of more than three months' duration and affecting more than one extrainguinal site in the absence of any other causative illness or drugs.¹⁶ Other clinical features include malaise, fever, and fatigue. Lymph node biopsy reveals a follicular hyperplasia only. A prospective review of 90 PGL patients, who were not, however, assayed for HIV, suggests that 17% developed AIDS after 3-13 months.¹⁷ The ophthalmic features of these patients have not been described to our knowledge.

It was decided to study prospectively a group of patients known to be HIV positive and diagnosed as having either PGL or AIDS to determine their ocular features and to assess their prognostic significance.

Patients and methods

Twenty-eight male homosexuals were referred for

Correspondence to R C Humphry, FRCS, West of England Eye Infirmary, Exeter, Devon.

ophthalmic review from St Mary's Hospital, London W1, to the Western Ophthalmic Hospital between April 1984 and December 1985. The examining ophthalmologist (RH) was unaware of whether the diagnosis was AIDS or PGL or whether the patient was HIV positive or not. The patients were ambulatory and relatively symptom free at the time of referral. No ocular symptoms or signs had been detected by the referring physicians.

A full ophthalmic history was taken, followed by an ocular examination, including Snellen's visual acuity, slit-lamp observation, and funduscopy after dilating the pupils with tropicamide 1%.

Results

Twenty-eight patients were assessed over an 18-month period. Their ages ranged from 23 to 53 years. Eighteen were diagnosed as having PGL and 10 as AIDS. Sixteen of the PGL and all of the AIDS patients were HIV-positive. They were reassessed at 3–4 month intervals for at least one year. At eight months five failed to attend follow-up, five had died, and one had presenile dementia. At one year 12 failed to attend follow-up and one more had died

(Table 1). Those who failed to attend follow-up did not acknowledge repeated letters inviting them for assessment and the letters were frequently returned unopened indicating that they had moved address.

The clinical findings are shown in Tables 2 and 3. Cotton wool spots were found in five of the 10 AIDS patients at some stage of their attendance (Figs. 1a, b, 2a, b). Two of these patients died within three months of a generalised cytomegalovirus (CMV) infection (cases 1 and 7) without any progression in their fundal features. The cotton wool spots of the remaining three patients had disappeared at the next three-month appointment and the patients remained well. However, at six months two of the patients had died of opportunistic pneumonia (cases 4 and 5) and one had developed HIV related encephalopathy and presenile dementia (case 2).

Cotton wool spots were found in one of the PGL group (case 26, Fig. 3). These were transitory. Six months later, however, the patient developed cotton wool spots again and a Roth spot while suffering from a severe *Mycobacterium avium* intracellular pneumonia and was diagnosed as having AIDS. The pneumonia did not respond to intensive therapy, and he died eight months after initial referral.

One of the AIDS patients with cotton wool spots developed an internuclear ophthalmoplegia secondary to a presumed brain stem CMV encephalitis at a terminal stage of his illness (case 1). At this stage an intraretinal haemorrhage was also noted (Fig. 1a).

One patient (patient 14) had suffered an attack of ophthalmic herpes zoster, with no permanent sequelae.

Six of the patients complained of tired, itching, or

Table 1 Failures, deaths, and dementia among 28 patients at four-monthly intervals

Follow-up period	Total failures	Total dead	Total dementia	Total remaining
4 months	4	3	1	21
8 months	5	5	1	17
12 months	12	6	1	9

Table 2 Ophthalmic features and diagnosis in the AIDS group

At presentation				During study period				
Patient number	Systemic features	Ocular complaints	Ocular signs	Ocular features	Systemic complications	Sequelae	Diagnosis	HIV seroassay
1	CMV encephalitis	Diplopia	Bilateral CWS	Internuclear ophthalmoplegia	CMV brainstem encephalomyelitis	Dead	AIDS	+ve
2	<i>Pneumocystis carinii</i> pneumonia	None	Bilateral CWS (transient)	CWS resolved	AIDS encephalopathy	Dementia	AIDS	+ve
3	Kaposi's sarcoma	None	None	'Tired eyes'	<i>Pneumocystis</i> pneumonia	Dead	AIDS	+ve
4	Cryptococcal pneumonia	None	None	Bilateral CWS (transient)	Cryptococcal meningitis	Dead	AIDS	+ve
5	Kaposi's sarcoma	'Tired eyes'	None	Bilateral CWS (transient)	Pneumonia	Dead	AIDS	+ve
6	Kaposi's sarcoma	None	None	Itchy eyes	None	Alive	AIDS	+ve
7	Toxoplasma cerebral abscess, candida	'Dry eyes'	Unilateral CWS	Status quo	Disseminated CMV and toxoplasmosis	Dead	AIDS	+ve
8	<i>Pneumocystis</i> pneumonia	None	None	None	'Tired'	Alive	AIDS	+ve
9	Kaposi's sarcoma	None	None	None	None	Alive	AIDS	+ve
10	Kaposi's sarcoma	None	None	None	None	Alive	AIDS	+ve

CWS=cotton wool spots.

Table 3 Ophthalmic features and diagnosis in the PGL group

At presentation				During study period				
Patient number	Systemic features	Ocular complaints	Ocular signs	Ocular features	Systemic complications	Sequelae	Initial diagnosis	HIV seroassay
11, 12, 13, 15, 17, 20, 23, 25, 27, 28	None	None	None	None	None	Alive	PGL	All +ve
14	Previous herpes zoster ophthalmicus	None	None	None	None	Alive	PGL	-ve
16	None	None	None	Non-bacterial conjunctivitis	None	Alive	PGL	+ve
18	None	'Aching eyes'	None	None	None	Alive	PGL	+ve
19	None	None	None	'Tired eyes'	None	Alive	PGL	+ve
21	None	None	None	None	Streptococcal pneumonia	Alive	PGL	+ve
22	None	None	None	'Tired eyes'	Diarrhoea	Alive	PGL	-ve
24	None	Recurrent sty	None	Hordeolum	None	Alive	PGL	+ve
26	None	None	Unilateral CWS (transient)	Bilateral CWS and Roth spots	AIDS <i>Myco. avium</i> intracellular pneumonia	Dead	PGL	+ve

aching eyes, while two suffered recurrent styes. There were no conjunctival lesions suggestive of Kaposi's sarcoma, though four of the AIDS patients had Kaposi's sarcoma elsewhere. The eyelids were normal, and there were no features of eczema.

One of the AIDS patients died from *Pneumocystis carinii* pneumonia without ocular signs (case 3). Four of the AIDS and three of the PGL patients complained of non-specific symptoms of aching, itching, or intermittent redness of the eyes. These features were not related to other AIDS complications.

Discussion

In our study the most frequent ophthalmic findings were cotton wool spots. Histological studies show that these are characteristic cytoid bodies.¹⁸ The same paper distinguishes cotton wool spots clinically from CMV lesions by their lack of enlargement and transitory duration during serial observations. Although such cotton wool spots may be unrelated to, or appear before or concurrently with CMV retinitis, their presence suggests a microvascular

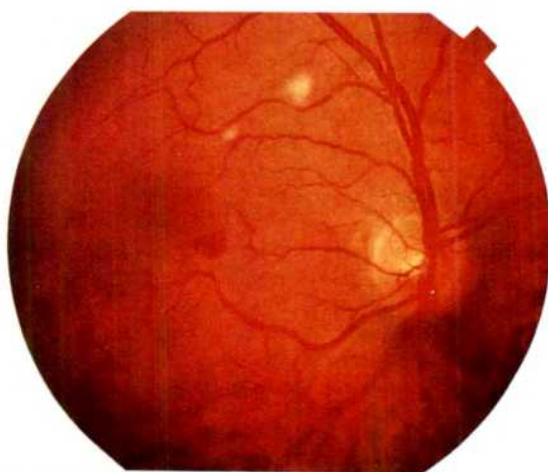


Fig. 1A

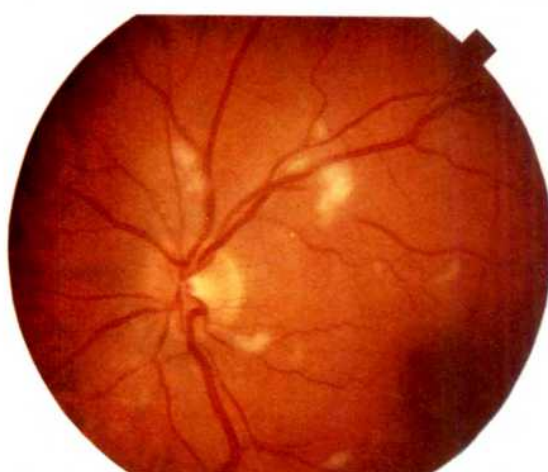


Fig. 1B

Figs. 1A, B Patient 1. Bilateral cotton-wool spots and right intraretinal haemorrhage in an AIDS patient who later died from CMV encephalomyelitis.

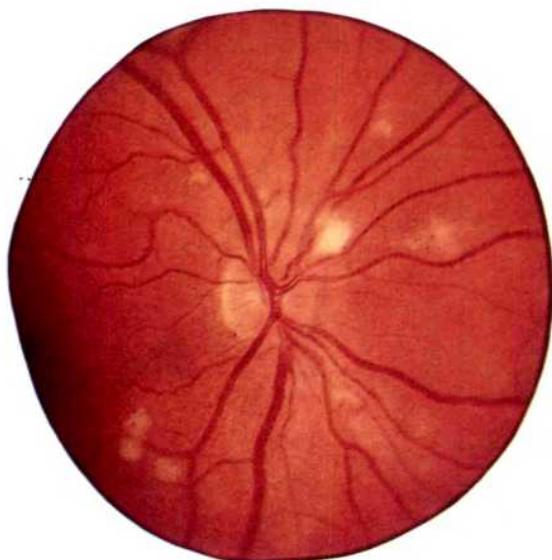


Fig. 2A

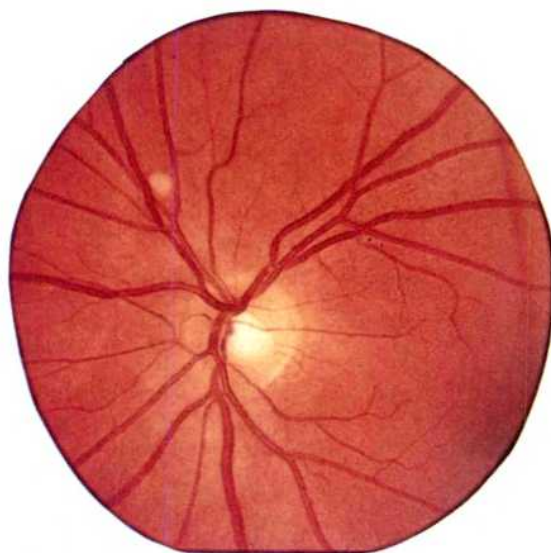


Fig. 2B

Figs. 2A, B Patient 2. Bilateral cotton-wool spots, which resolved three months later, in an AIDS patient who later developed AIDS encephalopathy and dementia.

alteration in AIDS, probably related to the high levels of circulating immune complexes found in the syndrome.¹² In a later study Pepose *et al.*¹⁹ proposed a mechanism linking the deposition of immune complexes to cause microvascular lesions resulting in ischaemia, axoplasmic stasis, and cotton wool spot formation. They further suggest that a CMV viraemia may lead to retinal infection via the

damaged vascular endothelium. Our five AIDS patients with cotton wool spots did not have coexisting diabetes, hypertension, or collagen vascular disease at the time of their examination. Two of these patients (1 and 7) died within three months of a generalised CMV infection that was diagnosed clinically and confirmed by laboratory studies.

Despite many studies there have been no reports of virus particles being detected in cotton wool spots.^{12,14,19} These cotton wool spots cannot be considered to represent an early CMV retinitis, since the lesions, while particularly florid in case 1, did not progress to the typical necrosis and haemorrhages, or 'cottage cheese and ketchup' appearance of CMV retinitis which we have seen previously in immunosuppressed or other hospitalised AIDS patients. The cotton wool spots were transitory in the remaining three. However, two patients (4 and 5) of these three died after six months, and the survivor (patient 2) had presenile dementia due to AIDS encephalopathy confirmed by computerised tomography.

The one PGL patient who developed a (transient) cotton wool spot progressed to AIDS within six months. The remaining 17 PGL patients and four AIDS patients were well after one year, and so cotton wool spots occurring independently of systemic disease must be assumed to carry a prognostic significance for preceeding opportunistic infections in both groups of patients. The one patient with an ocular motility disorder had a CMV encephalitis, confirming reports of the severity of this clinical feature.¹²

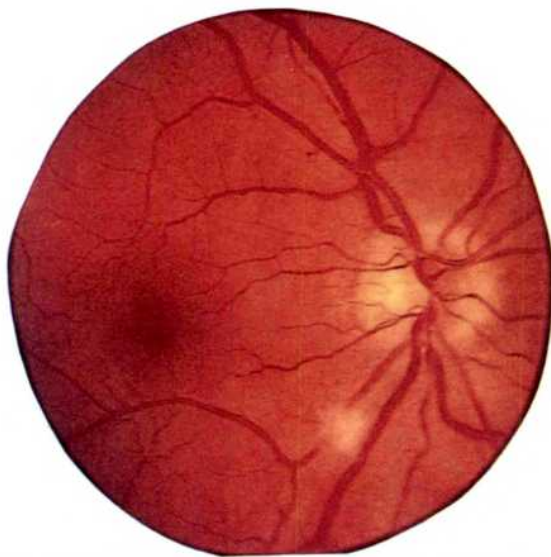


Fig. 3 Solitary cotton-wool spot in the right eye of a patient with PGL who developed AIDS six month later (see text).

Irritation and itching of the eyes were common in both groups of patients but bore no relationship to the disease state or prognosis. HIV has been isolated from the tears,²⁰ but there have been no studies to our knowledge of the tear production or profile in such patients.

The involvement of the ophthalmologist with HIV and AIDS related diseases may be varied. An ophthalmologist may be the first to examine an AIDS or pre-AIDS patient with ocular features and may hence assist in the early diagnosis. Indeed this has already occurred at the Western Ophthalmic Hospital. In already diagnosed cases of AIDS or PGL the ophthalmologist may assist in the early detection of ensuing complications, since our results suggest that cotton wool spots act as a 'marker' for patients at risk of early admission to hospital and death. Although, at present, few patients survive more than four months from the onset of CMV retinitis,^{12,15} this is a major form of visual loss in AIDS. As therapy for generalised opportunistic infections improves, it is likely that the ophthalmologist will be asked to assess increasing numbers of visually handicapped patients, since the treatment of CMV retinitis is still undergoing trials.^{21,22}

We thank Dr A J Pinching and Dr J R W Harris for allowing us to examine their patients, Sue Ford for taking the fundus photographs, and Eleanor Beric for performing the HIV assays; also to Dr D J Jeffries for critically reviewing this manuscript.

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Histological study of corneas preserved in two new media

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SUMMARY A new corneal preserving medium (K-Sol), developed by Kaufman and others, contains purified chondroitin sulphate, TC 199, HEPES buffer, and gentamicin. Another new medium (JM) containing bicarbonate-free glucose-phosphate Ringer solution and dextran 70 has been developed in Japan. New Zealand white rabbit corneas with scleral rims were stored in each medium at 4°C for one or two weeks. The condition of the endothelium was evaluated histologically. Corneas preserved in both media were in good condition at the end of one week. Corneas preserved in K-Sol for two weeks showed fewer endothelial changes than similar tissue stored in JM for two weeks. Corneal swelling was also less in corneas preserved in K-Sol, than in corneas preserved in JM.

Many eye banks now use M-K medium, which was developed in the United States by McCarey and Kaufman in 1974 to preserve donor corneas until surgery. M-K medium maintained viability (as measured by temperature reversal) of rabbit corneal endothelium and generally preserved rabbit corneas for up to 14 days.¹ However, clinical results with human corneas suggested that storage time in M-K medium should be limited to three or four days.²

Recently Kaufman and others developed a new corneal preservation medium (K-Sol). Corneas stored in this new medium have been tested in animal studies and used in human corneal transplants. Corneas stored in K-Sol have been successfully transplanted following storage for up to two weeks.^{3,4}

Mizukawa and associates⁵ in 1968 developed a new liquid preserving medium, consisting of a mixture of TC-199, NaHCO₃, 1.5% chondroitin sulphate, inosine, adenine, adenosine, streptomycin, and penicillin. This medium was used as a corneal preserving medium in Japan. Mayes *et al.*⁶ reported that rabbit corneas stored in medium with a low bicarbonate concentration functioned better than corneas stored in medium with high bicarbonate concentration. Based on these findings a new corneal preservation medium (JM) was developed, and Manabe *et al.*⁷ have reported that this new medium is

an excellent and safe corneal storage medium for clinical usage.

In this study, corneas with scleral rims were stored in JM and in K-Sol, and the condition of the endothelium was evaluated histologically.

Materials and methods

PRESERVING MEDIUM

The Japanese medium (JM) (Kaken Pharmaceutical Company, Hongo, Tokyo) named EP-II is based on bicarbonate-free glucose-phosphate Ringer's solution and contains dextran 70, a few electrolytes, and a mixture of streptomycin and penicillin. The medium has an osmolarity of 305 mosm and pH of 7.40 (Table 1).

Table 1 *Japanese Medium (JM)*

Component	Concentration
Glucose phosphate Ringer (HCO ₃ ⁻ free)	
No CaCl ₂	
No MgCl ₂ ·6H ₂ O	
Dextran 70	3.5%
Na-citrate·2H ₂ O	900 µg/ml
MgSO ₄ ·7H ₂ O	218 µg/ml
Streptomycin sulphate	1000 µg/ml
Potassium penicillin G	200 units/ml
pH	7.40
Osmolality	305 mosm

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Table 2 K-Sol

Component	Concentration
TC 199	
HEPES buffer	0.25 M
Chondroitin sulphate, purified MW >10000	2.5%
Gentamicin sulphate	100 µg/ml
pH	7.40
Osmolality	310 mosm

K-Sol contains 2.5% purified chondroitin sulphate (molecular weight >10000) in TC 199, 0.25 M HEPES buffer, and gentamicin sulphate (Cilco, Sanford, NC). The medium has an osmolality of 310 mosm, and a pH of 7.40 (Table 2).

TISSUE

New Zealand white rabbits were killed with an overdose of sodium pentobarbital and both eyes were immediately enucleated. Corneas with scleral rims

were stored in either JM or K-Sol at 4°C. Eight pairs of corneas were used: the right corneas were preserved in JM and the mate corneas were preserved in K-Sol. Four pairs of corneas were stored for one week, and another four pairs were stored for two weeks at 4°C.

MICROSCOPY

At the end of the period of observation the specimens were divided into two pieces. One part was fixed immediately in 2.5% glutaraldehyde and 3% formalin with 1/15 M potassium sodium phosphate buffer (pH 7.35) for 12 hours, washed in the same buffer, postfixed in buffered 1% osmium tetroxide for 90 minutes, washed again in buffer, dehydrated in graded alcohols from 50% to 100% and propylene oxide, and embedded in Epon. Embedded specimens were sectioned with a microtome and stained with toluidine blue for light microscopy or uranyl acetate and lead citrate for transmission electron microscopy.

The other part of each cornea was fixed in 2.5%

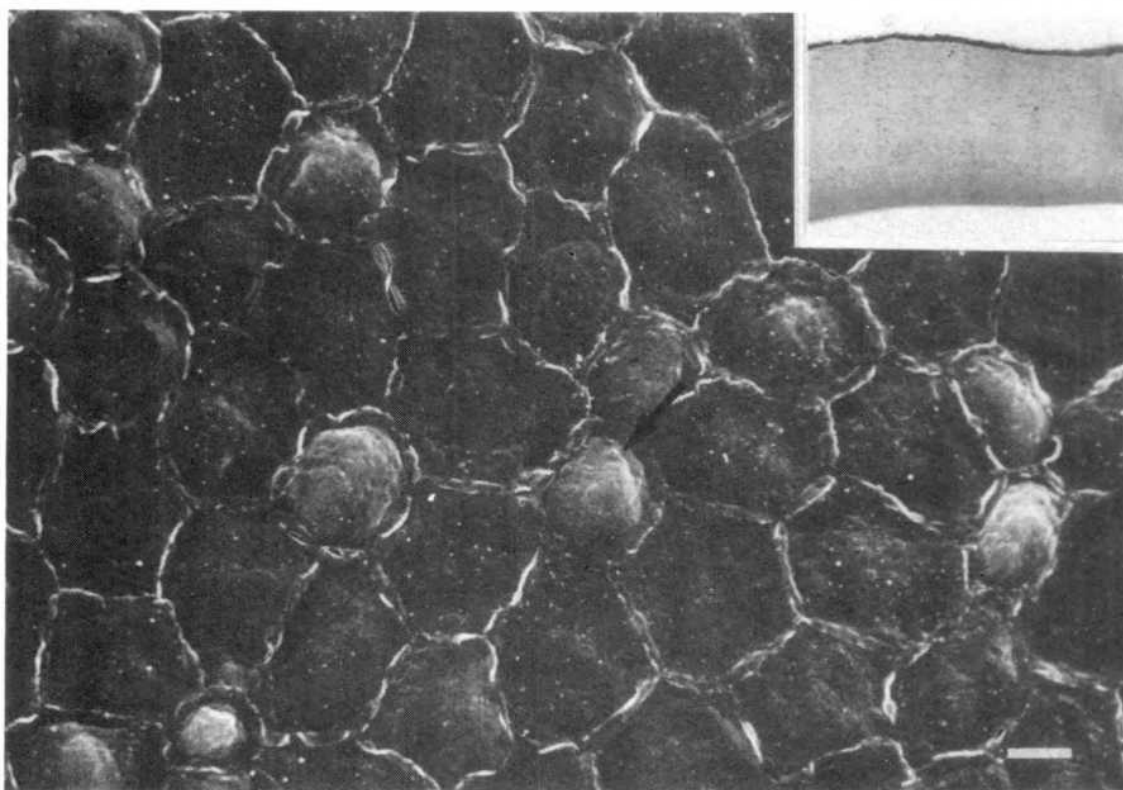
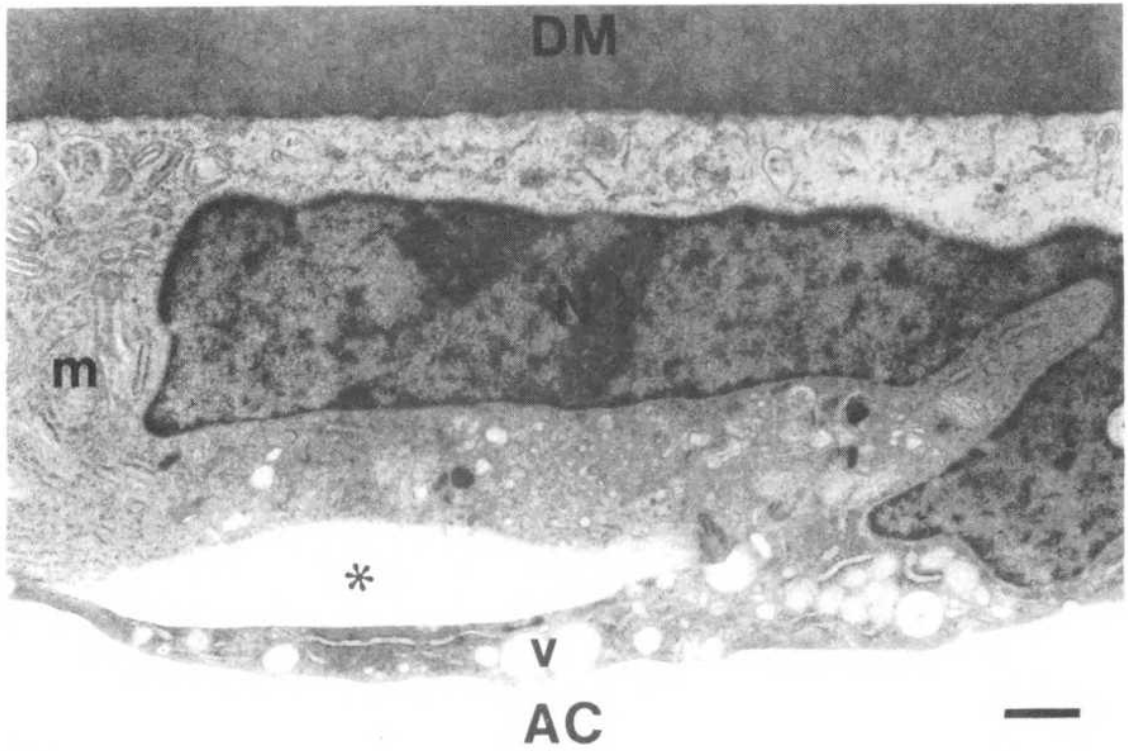
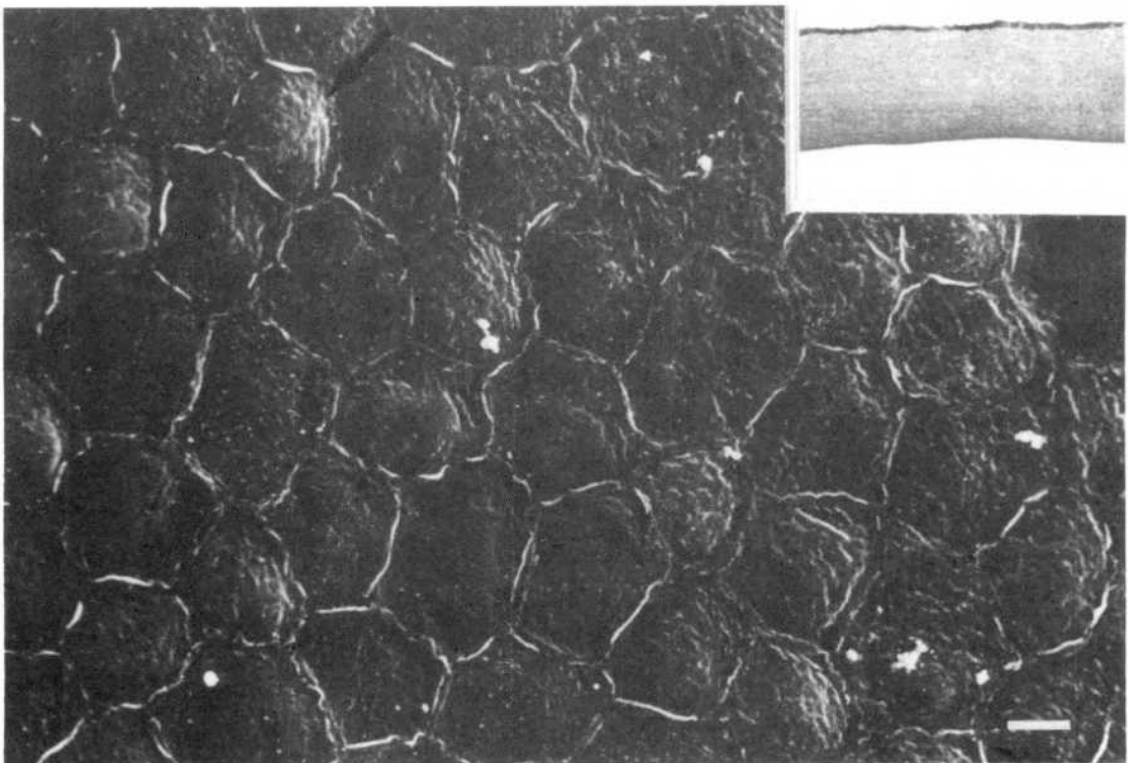


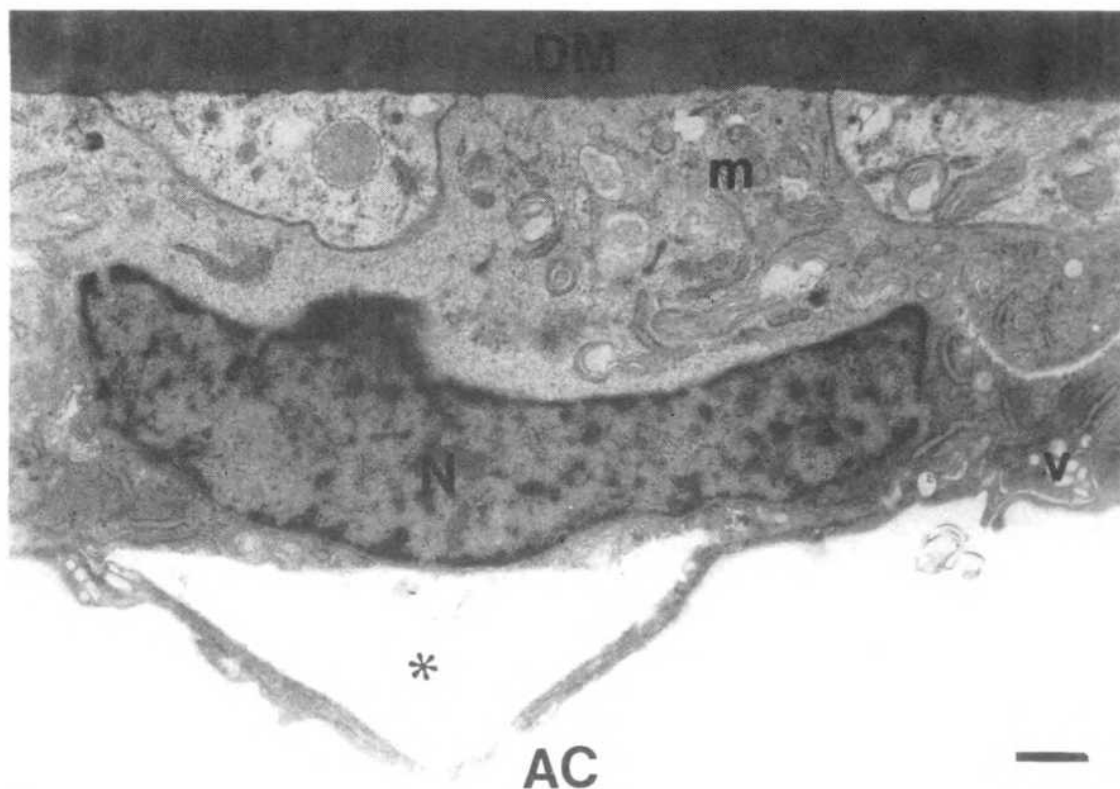
Fig. 1A JM preservation for one week. Scleral rim. Scanning electron micrograph of the corneal endothelium. Some of the endothelial cells are swollen and protruding (arrow). Normal mosaic-like appearance can be seen. Bar = 5 µm. Inset: Light micrograph. Corneal thickness is 0.56 mm. Corneal swelling is prominent. The epithelial cells and stromal cells are well preserved. Toluidine blue.



1B



2A



2B

glutaraldehyde and 3% formalin with potassium-sodium buffer (pH 7.4) for 12 hours, dehydrated in alcohol, dried in a critical-point dryer, placed on aluminum stubs, coated with gold, and photographed by means of scanning electron microscopy. Corneal thickness was measured on light micrographs, which were enlarged 30 times.

Results

The appearance of the preserved corneas was similar in all specimens.

PRESERVATION FOR ONE WEEK

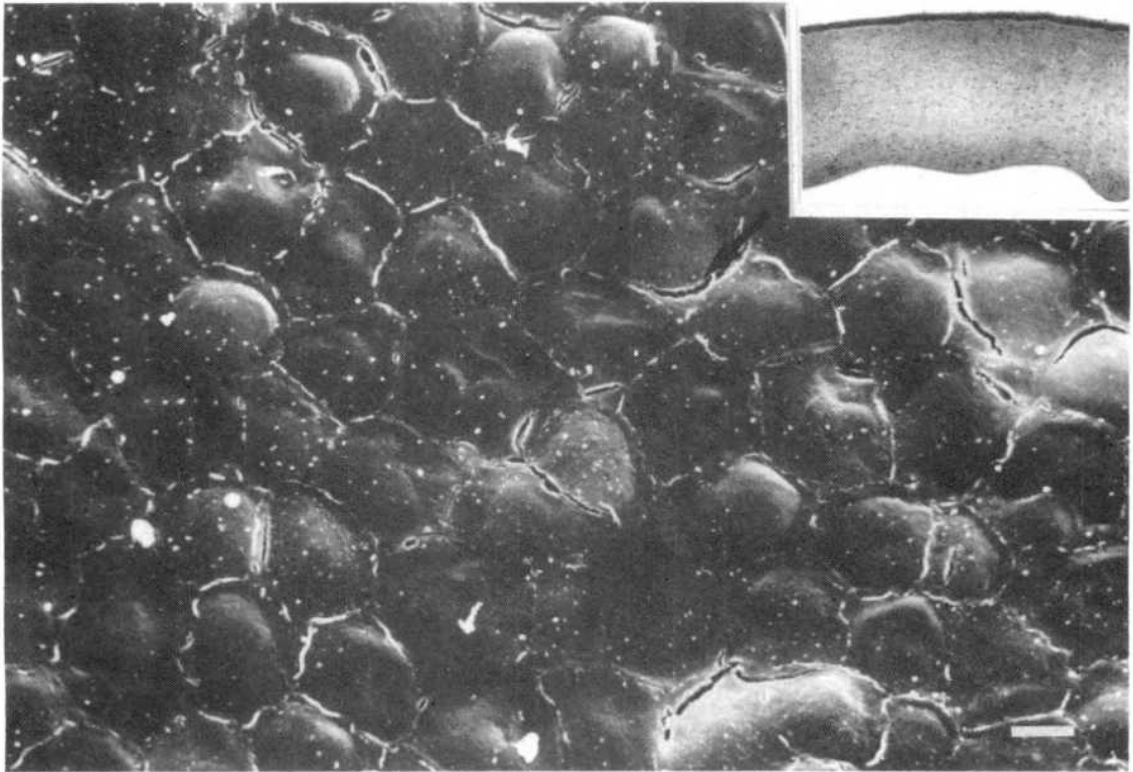
On light micrographs the average thickness of the corneas preserved in JM was 0.54 mm and stromal swelling was prominent (Fig. 1A, inset). The control corneal thickness was 0.31 mm. The corneas preserved in K-Sol (Fig. 2A, inset) measured 0.39 mm in thickness, and no stromal swelling was seen. The epithelial cells were intact and the stromal cells were preserved in both corneas.

Both corneas appeared similar by scanning electron microscopy. A few swollen endothelial cells were seen protruding into the anterior chamber.

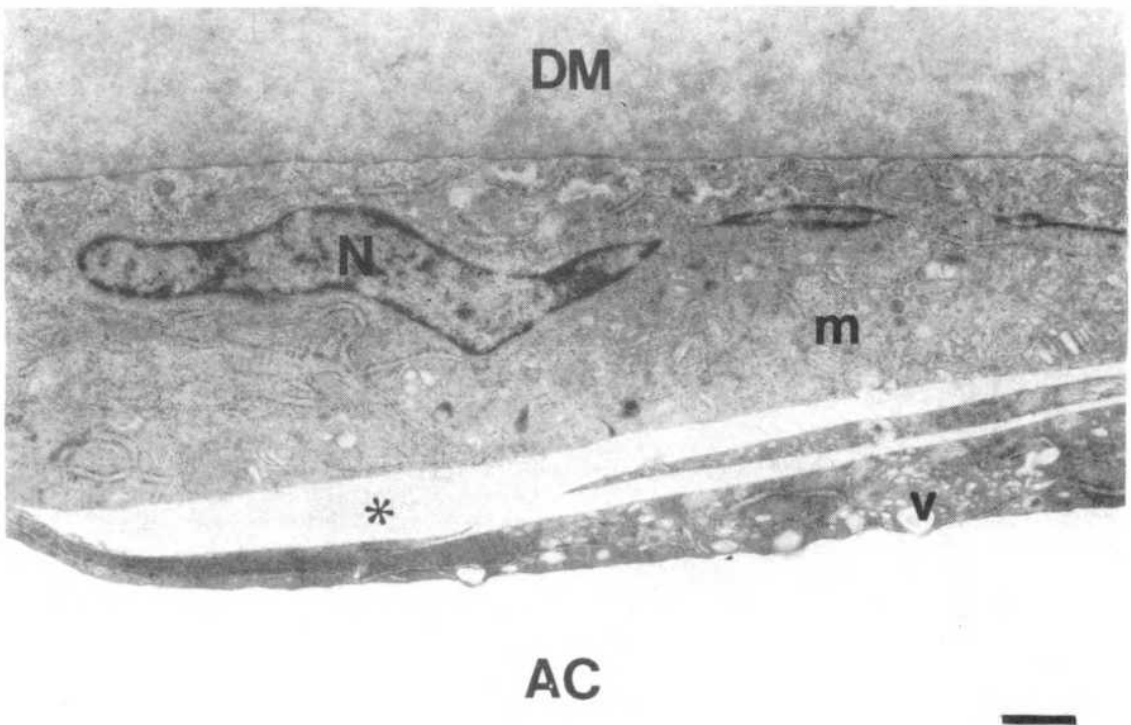
Fig. 1B JM preservation for one week. Scleral rim. Transmission electron micrograph of same cornea as in Fig. 1A. Cleft (*) and small vacuolations (V) can be seen on the apical side. The cytoplasm is slightly less dense anterior to the nucleus. The cytoplasmic organelles are almost intact. DM=Descemet's membrane; N=nucleus; AC=anterior chamber; M=mitochondria. Bar=0.7 μ m.

Fig. 2A K-Sol preservation for one week. Scleral rim. Scanning electron micrograph of the corneal endothelium. A few endothelial cells (arrow) are swollen. Normal mosaic-like appearance can be seen. Bar=5 μ m. Inset: Light micrograph. Corneal thickness is 0.40 mm. The stroma is not swollen. The epithelial cells and stromal cells are well preserved. Toluidine blue.

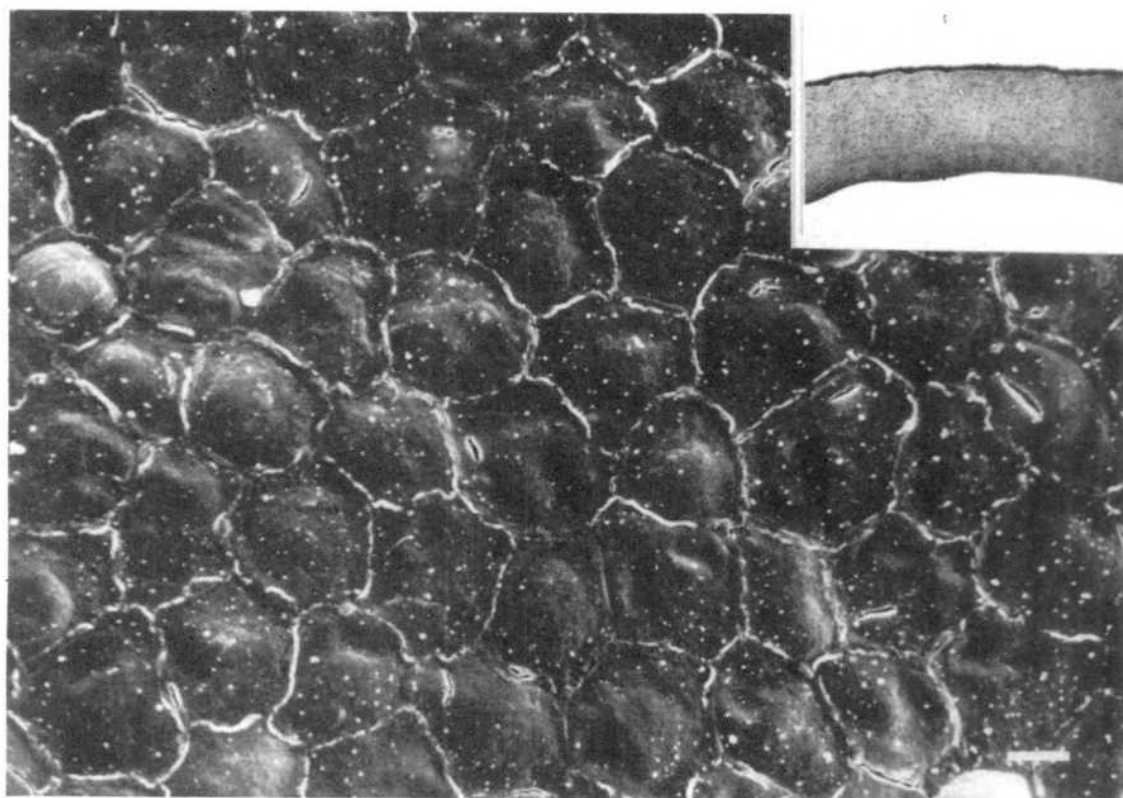
Fig. 2B K-Sol preservation for one week. Scleral rim. Transmission electron micrograph of the same corneas as in Fig. 2A. Cleft (*) and a few vacuolations (V) can be seen. Cytoplasmic organelles are almost intact. DM=Descemet's membrane; N=nucleus; M=mitochondria; AC=anterior chamber. Bar=0.7 μ m.



3A



3B



4A

Intercellular cytoplasmic membranes were distinct. The mosaic-like arrangement of the hexagonal endothelial cells was nearly normal (Figs. 1A, 2A).

By transmission electron microscopy the corneas also looked similar. An endothelial cleft and small vacuolations were seen. The cytoplasm seemed less dense anterior to the nucleus. The mitochondria were somewhat swollen, but the cristae were not disrupted (Figs. 1B, 2B). The endothelial sheets were preserved in good condition.

PRESERVATION FOR TWO WEEKS

On light micrographs the average thickness of the

corneas preserved in JM measured 0.53 mm, and stromal swelling was prominent (Fig. 3A, inset). The thickness of the cornea preserved in K-Sol was 0.35 mm, which is almost normal (Fig. 4A, inset). The epithelial cells and stromal cells were well preserved in both corneas.

By scanning electron microscopy corneas preserved in JM showed some swollen endothelial cells protruding into the anterior chamber, and cellular pleomorphism was prominent. Several pits were seen in the intercellular junctions (Fig. 3A). The corneas preserved in K-Sol showed a few swollen endothelial cells and small pits in the cytoplasmic membrane.

Fig. 3A JM preservation for two weeks. Scleral rim. Scanning electron micrograph of the corneal endothelium. About 20% of the endothelial cells are swollen and cellular pleomorphism is prominent. Pits (arrow) can be seen on the surface of the endothelium. Mosaic-like appearance can still be seen. Bar=5 μ m Inset: Light micrograph. The epithelial cells and stromal cells are well preserved. Corneal thickness is 0.54 mm. Corneal swelling is prominent. Toluidine blue.

Fig. 3B JM preservation for two weeks. Scleral rim. Transmission electron micrograph of the cornea seen in Fig. 3A. Large clefts (*) and small vacuolations (V) can be seen on the apical side of the endothelium. The cytoplasmic organelles are intact. DM=Descemet's membrane; N=nucleus; M=mitochondria; AC=anterior chamber. Bar=0.7 μ m.

Fig. 4A K-Sol preservation for two weeks. Scanning electron micrograph of the corneal endothelium. The intercellular cytoplasmic membranes are distinct, and the hexagonal endothelial cells demonstrate a normal mosaic-like appearance. A few swollen endothelial cells and pits can be seen. Bar=5 μ m. Inset: Light micrograph. Corneal thickness is 0.35 mm. No stromal swelling is seen. The epithelial cells and stromal cells are well preserved. Toluidine blue.

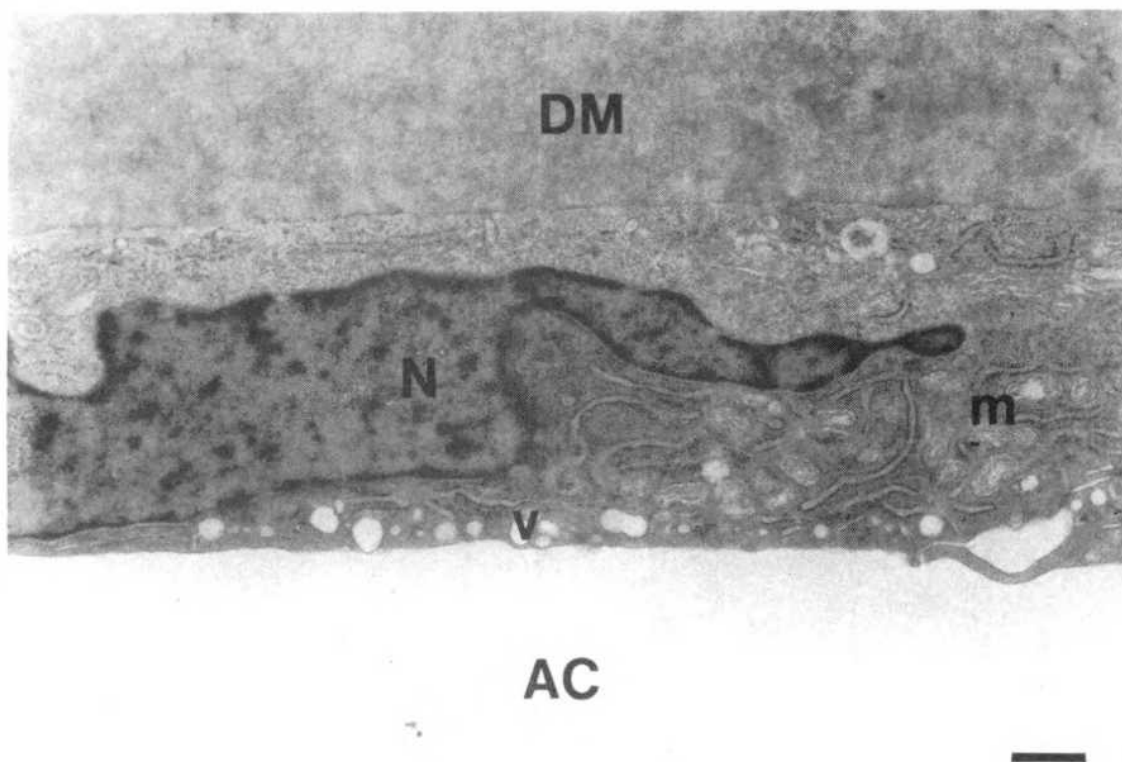


Fig. 4B K-Sol preservation for two weeks. Scleral rim. Transmission electron micrograph of the same cornea seen in Fig. 4A. A few small vacuolations can be seen. Cytoplasmic organelles are intact. DM=Descemet's membrane; N=nucleus; M=mitochondria; AC=anterior chamber. Bar=0.7 μ m.

The intercellular cytoplasmic membranes were well preserved, and the hexagonal endothelial cells demonstrated a normal mosaic-like appearance. The endothelial sheets were almost intact (Fig. 4A). By transmission electron microscopy the corneas preserved in JM showed large clefts and small vacuolations. The cytoplasmic organelles were almost normal (Fig. 3B). In the corneas preserved in K-Sol the endothelial cells were almost intact except for small vacuolations (Fig. 4B).

Discussion

JM, which contains no bicarbonate, was developed by modifying glutathione bicarbonate Ringer's solution (GBR).⁸ Endothelial function is almost stopped by cooling to 4°C. Mayes *et al.*⁹ reported that a preserving medium with low bicarbonate concentration intensifies this effect. Therefore, nutritional materials are not included in this medium except for glucose. In contrast, K-Sol contains tissue culture medium for corneal nutrition, though K-Sol preser-

vation also reduces corneal endothelial function by cooling to 4°C.

Because cooling of the cornea to 4°C stops the function of the corneal endothelium, it also triggers corneal swelling. Dextran 70 and chondroitin sulphate are both high molecular weight materials that prevent stromal swelling.⁹⁻¹¹ JM contains dextran 70 (MW 70 000) and K-Sol contains purified chondroitin sulphate (MW >10 000). For penetrating keratoplasty it is desirable to use grafts of normal thickness. In our experiments corneas with scleral rims preserved in K-Sol maintained normal thickness for up to two weeks. No stromal swelling was seen (Fig. 4A). However, corneas with scleral rims preserved in JM were thicker than those in K-Sol and stromal swelling was prominent (Fig. 3A); thus K-Sol preservation appears to be superior in preventing stromal swelling. It is believed that purified chondroitin sulphate prevents corneal swelling, as first reported by Kida.⁹

Characteristic changes seen by transmission electron microscopy in the endothelium were clefts,

cytoplasmic vacuolations, and decreased cytoplasmic densities. The clefts were parallel to the cytoplasmic membrane and crescentic in shape. Small vacuolations were located on the apical side. Similar changes have been reported in the past with 4°C preservation.^{11,12} Sakimoto *et al.*¹² reported that the clefts disappeared after penetrating keratoplasty. This change may be the result of the loss of endothelial function during 4°C preservation. The density of the cytoplasmic organelles was somewhat decreased in the endothelial cells, but the organelles were almost intact. Overall, the endothelial sheets were in good condition in both corneas preserved for two weeks, though nearly all the endothelial cell nuclei were swollen.

By scanning electron microscopy the changes seen in endothelial cells preserved in both media for one week were negligible. Endothelial cell size was normal and the cytoplasmic membranes were almost intact (Figs. 1B, 2B). Corneas preserved for two weeks showed no endothelial cell loss. The hexagonal cells were well preserved. However, a few endothelial cells were enlarged, and endothelial pleomorphism was prominent. Endothelial swelling and pits in the cytoplasmic membrane were also visible, though the cytoplasmic pits were not confirmed by transmission electron microscopy. These endothelial changes (pleomorphism and pits) were more prominent in the corneas preserved in JM. Mizukawa *et al.*⁵ reported that even at 4°C the function of the cornea cannot be stopped completely; therefore a preserving medium should contain some nutritional additives. It is conceivable that lack of nutrition results in more changes in corneas preserved in JM, and that chondroitin sulphate exerts a beneficial effect on corneal endothelial cells preserved in K-Sol, as reported by Lindstrom and associates.¹³

K-Sol preserved corneas have been used in corneal transplantation in humans with good results.⁴ Human corneal endothelium degenerates much faster than that of rabbits,⁶ and the reproductive power of the endothelium in the rabbit is much greater than in humans. Therefore it seems likely that the results

obtained with rabbit corneas in this study are better than those obtained with human tissue. However, it may also be true that some histological changes that may occur in human tissue during storage may be reversible when the cornea is transplanted into the eye. In this study, although the corneas with scleral rims preserved for two weeks in both K-Sol and JM remained in good condition, somewhat better results were obtained with K-Sol.

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Blindness in schoolchildren: importance of heredity, congenital cataract, and prematurity

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SUMMARY Of 99 children in the Royal Blind School, Edinburgh (which serves Scotland and part of N E England), 15 had optic atrophy (hydrocephalus 4, intracranial haemorrhage 2, prematurity 2, fetal distress 2, birth asphyxia 2, cerebral atrophy 1, cardiac arrest during hernia operation 1, and leukaemia 1). Fourteen had congenital cataract, 12 congenital retinal aplasia (Leber's congenital amaurosis) and 11 retinopathy of prematurity. There were small numbers in many other diagnostic categories, including three with non-accidental head injury. Mental retardation, spasticity, and nystagmus were frequent other correlates in all diagnostic categories. 'Very probably hereditary' was a conservative attribution in 36, while 'probable' seemed appropriate for 12 - that is, almost 48% were hereditary. Only about 11 cases might have been prevented through genetic counselling, which testifies to the frequency of autosomal recessive hereditary disease, although no parents were consanguineous.

The Royal Blind School (RBS), Edinburgh, is a residential school for the severely visually handicapped with a visual acuity almost invariably 3/60 or less or, occasionally, with very severe field loss. Our diagnostic survey of its 99 pupils does not include all Scottish blind children of school age, because educability is another criterion for admission, though many of the pupils are mentally retarded, some quite severely so. We have no information about blind children in other institutions for the very severely (multiply) handicapped. The only other school for the blind in Scotland is a small one in Glasgow: it has few residents, and caters for the deaf and the blind-deaf as well as some blind. The catchment area of the Edinburgh school also includes the north of England, especially the north-east, since a blind school in

Newcastle upon Tyne closed; six pupils have present home addresses in England.

This survey of the RBS is more comprehensive than our previous statistics of only hereditary cases there.¹ Another motive for the study was to compare the diagnoses in Scotland with those in 67 pupils in the Blind School of Yamanashi Prefecture, 120 km south-west of Tokyo, Japan.² One common observer in each study should make comparisons reasonably valid. The present information is also a selective update of the comprehensive survey of 776 blind children in England and Wales by Fraser and Friedmann published in 1967³ and of Sorsby's study of blindness in all age groups for 1963-8 in the same countries⁴ and of the Report of the Department of Health and Social Security for England 1969-76.⁵

Material and methods

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Permission to be included in this survey was obtained from the parents of all except two pupils. Ages

ranged from 5 to 18 years. Each pupil was fully examined and the case records at the Royal Blind School scrutinised. Binocular indirect ophthalmoscopy was often essential. Supplementary information was sometimes required from hospital records. A few patients were very difficult to examine, especially when mentally handicapped, even though the children and parents tried hard to be co-operative. In them more reliance was placed on records of previous examinations under anaesthesia and electro-diagnostic tests. The family history was obtained from parents, case records at the Royal Blind School or hospital, teachers, or our own records in our ophthalmic genetics clinic. Several children and families were already known to us in detail.⁶⁹

Results

The large amount of information collected has been condensed into Table 1. The main cause of blindness has determined the classification, but some important coexistent abnormalities, ophthalmic and general, are mentioned in the last column headed 'Comments and complications.' Nystagmus was so frequent a complication that it is mentioned only in the two females in whom it was the primary cause of visual handicap.

'Optic nerve atrophy' was applied to 15 cases, but it was further divided into numerous smaller subgroups with a more fundamental diagnosis. Four cases of optic atrophy have been separately listed under injury, head, and one each under brain tumour and abscess. Of the 15 cases included under 'optic nerve atrophy' hydrocephalus accounted for four, non-traumatic intracranial haemorrhage for two (one premature and one with pencephaly,) prematurity for two, and fetal distress and birth asphyxia for two each, although at least one of the last may have had a more basic correlate, microcephaly. One each was attributed to cerebral atrophy, cardiac arrest during a hernia operation (a definitely iatrogenic disease), and leukaemia with or without virus infection or its drug treatment. Optic nerve hypoplasia (one) is not included in these 15.

There were 12 cases of congenital cataract, almost all operated upon in infancy. The mendelian dominant cases (four) seem to have fewer associated systemic diseases than the sporadic (six) or adopted (two) ones.

Another 12 cases were classified under retinal aplasia (Leber's congenital amaurosis), often with other handicaps (Table 1).

Ranking third of the single clinical entities (apart from the optic atrophy 'group' above), and closely rivalling congenital cataracts at 12 cases and retinal aplasia at 12 cases, was retinopathy of prematurity

with 11 cases. Of these, seven were mentally retarded with other serious correlates (see last column of Table 1), while three others had other serious complications but not mental retardation; Table 2 presents their birth weights, and Table 3 relates birth weights to intelligence quotient (IQ) and sex.

Only three cases of aniridia were definitely dominant. It is interesting that three of the four sporadic cases had the syndrome of a deletion of the short arm of chromosome 11 and mental retardation; one of these three also had a Wilms tumour.

Under the diagnosis 'injury, head' are a minimum of three with definitely non-accidental trauma. The possibility exists in more than one other case, but the evidence was not good enough to be certain of that cause. One patient was probably blinded indirectly by epilepsy, through head injury.

Although the numbers with other diagnoses are small (Table 1), they make up in sum a significant proportion of the pupils, of special interest because many are hereditary in origin (see 'Discussion').

Table 4 presents a classification by hereditary pattern when present. In 40 cases there was not even a suspicion of a hereditary cause. 'Very probable,' however, is a conservative description of the level of likelihood in 36; 'probable' seemed reasonable in 12; 'possible' (five) and 'suspected' (five) made up the balance of 58. (The 99th patient with cataract associated with Rh factor haemolytic disease was not classified as either genetic or non-genetic.)

Discussion

At the beginning of each session we survey new admissions to this blind school for hereditary disease. Parents may have completed their families by the time a blind child is old enough for school education, so that genetic counselling, if appropriate and not already given, is usually superfluous. Towards the end of each session we see the school leavers to offer genetic information if consent is given; it is also important for teenagers who do not have hereditary disease to be reassured on that score. Parents are also invited to attend these sessions with their teenage children, but very few do so.

We had the impression of a high prevalence of hereditary disease at various levels of probability in these children. Hence the decision to make this comprehensive survey of all pupils at the school throughout session 1984-5. We rate 36 of the 99 pupils as having 'very probable' hereditary disease, 12 as 'probable,' while another 10 are either 'possible' (five) or 'suspected' (five) (Tables 1 and 4). Accordingly heredity is responsible for between 48 and 58 of the 99 blind pupils at this school.

Mainly because so many cases are (very) probably

Table 1 Causes of blindness: diagnosis and heredity

Diagnosis	Number of cases: female/male (% almost the same since the total no. of pupils is 99)		Heredity (+) += (very) probable ± = possible -- = non- hereditary chr = chromosome abnormality	Mendelian type: AD = autosomal dominant AR = autosomal recessive X = X-linked (?) = (very) doubtful	Comments/complications MR = mentally retarded (or retardation)
	F	M			
Albinism, ocular		2	++	X-linked	Brothers
Aniridia, dominant	2	1	++	AD	1F; mother affected 1M 1F sibs; mother affected
sporadic	2	1	++ chr	1M ?AR 1M, 2F, deletion short arm chromosome 11	2F 1M have MR, 1F has nephroblastoma
Anophthalmos, sporadic		3	+	?AR ('all sporadic')	1 has MR
Behçet's disease	„	1	—	—	—
Brain tumour	„	1	—	—	1M has craniopharyngioma 1F has abscess
abscess					
Cataract, congenital (12) dominant (4)	1	3	++	AD	4 have mother affected 1M has L microcornea 1F has father with retinitis pigmentosa 1 has half-brother affected 1M has parents divorced, MR
adopted (2)		2	?	?	
sporadic (6)	1		+	?AR	
+ Down's syndrome		1	chr	trisomy 21	MR
+ haemolytic disease at birth	1		(±)	Rh factor	Rh— mother, child +ve
lamellar		1	?	?AR	MR, spastic, cortical blindness
+ macular degeneration		1	?	?AR	MR has ataxic diplegia
rubella, maternal	1		—	—	MR has microcornea
Coloboma	2		+	?AR (sporadic)	1 has fundus involved, 1 with microphthalmos
Cone-rod dystrophy		1	++	AR	Keratoconus and lens opacities
Cortical blindness	2	3	—	—	1F choking fit at 7/12→ anoxia, cerebral palsy, M 1M cause unknown, also optic atrophy, MR 1F had postnatal hypoxia with visual agnosia, MR 1M has MR, premature birth, seizure, gastroenteritis 1M has microcephaly, spastic quadriplegia, MR
Glaucoma, congenital	1	1	++	AR	1F bilateral enucleation
Injury, head epileptic		1	—	—	MR, subdural haematoma optic atrophy: ? after fit
non-accidental	1	2			1F, 2M have subdural haematoma, optic atrophy, MR
Keratoconus	1		+	?AR	Allergic kerato- conjunctivitis
Macular degeneration 'coloboma,' that is, foveal dysplasia with retinal aplasia	1		+	?AR	—
with retinal aplasia		2	++	AR	1M brother affected
Microphthalmos		2	+	?AR ?? X-LR (both sporadic)	1 has congenital cataract 1 has microphthalmos: has one side anophthalmos
Norrie's disease		1	++	X-linked R	Brother affected

Table 1 Causes of blindness: diagnosis and heredity (continued)

Diagnosis	Number of cases: female/male (% almost the same since the total no. of pupils is 99)		Heredity (+) += (very) probable ± = possible -- = non- hereditary chr = chromosome abnormality	Mendelian type: AD = autosomal dominant AR = autosomal recessive X = X-linked (?) ? = (very) doubtful	Comments/complications MR = mentally retarded (or retardation)
	F	M			
Nystagmus	2		+	?AR	1F had birth asphyxia, deaf, ? albinoid fundus
?Solar burn	1		—	—	R affected (L strabismic amblyopia)
Optic nerve (see also head injury and brain tumour) hypoplasia	1		±	?AR	
atrophy (15) birth asphyxia		2	—	—	1M has cortical blindness (VER absent: ERG normal), caesarean birth after prolonged labour, microcephaly, 1M spastic, epileptic, bilat, VI nerve palsy, MR
cardiac arrest in hernia operation + cerebral atrophy fetal distress	1	1 2	— ?	— ?	1F MR 1M has MR, caesarean birth after prolonged labour 1M epileptic
hydrocephalus	1	3	—	—	1M has spina bifida, paralysis of lower limb 1F has meningococci
intracranial haemorrhage		2	—	—	1M had premature birth, diplegia and epilepsy, MR 1M has porencephaly, MR
leukaemia ± virus encephalitis	1		—	—	?Treatment of leukaemia caused optic atrophy
prematurity	1	1	—	—	1M weighed 1134 g at birth; EEG abnormal, MR 1F has spastic diplegia, ?MR
Retina aplasia (Leber's congenital amaurosis)	5	7	++	AR	2F and 3M have MR (incl. 1M hypothyroid and 1M cerebral palsy) 1M myopic 1F has sister affected
Bardet-Biedl syndrome fold, retinal		1 1	++ ++	AR AR	Polydactyly, myopia L total detachment, enucleation
non-attachment, bilateral retinoschisis		1 1	++ ++	AR X-linked	Not premature 2 Brothers affected; typical family history
retinitis pigmentosa	1		++	X-linked	Affected carrier; typical family history
	1		++	AR	Sister affected
retinoblastoma		1	++	AR	Deaf: Usher's syndrome
retinopathy of prematurity	2	9	—	—	Osteosarcoma of leg: amputated 4M have MR (incl. 1 diplegic, 1 ataxic and 1 cataract) 1 cataract, 1 twin died, 1 ataxia diplegia, 1 patent ductus Birthweights 709–1503 g
Septo-optic dysplasia		1	—	—	MR

Table 2 *Retinopathy of prematurity*

<i>Year of birth</i>	<i>Number</i>	<i>Birth weight in g</i>
1966	1	1304
1967-70	0	—
1971	3	1304, 1474, 1503
1972	2	709, 1361
1973 and 74	0	—
1975	1	907
1976 and 77	0	—
1978	1	998
1979	2	<907, 992
1980	1	1247

Table 3 *Birthweight and IQ*

<i>Birth weight</i>	<i>Total</i>		<i>Low IQ</i>		<i>Normal IQ</i>	
	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>
<2.5 kg	7	15	3	12	4	3
≥2.5 kg	26	45	7	16	19	29
Not known	1	5	—	4	1	1
Totals	34	65	10	32	24	33

autosomal recessive in causation (42), few could be said to be preventable by the parents' refraining from having children. Only the seven dominant cases, and possibly one of the two with X-linked ocular albinism, the X-linked retinoschisis, the X-linked retinitis pigmentosa, and the case of autosomal recessive retinitis pigmentosa might have been avoidable through genetic counselling. The boy with Norrie's disease and his younger brother, also affected but not yet at school, probably had inherited a mutation from his mother.⁶ The girl from a family with definite X-linked retinitis pigmentosa¹ may be showing a surprisingly severe manifestation of the carrier

state. Her mother is a carrier, but the girl's electroretinogram (ERG) is not typical, and high myopia is a factor in her 'blindness'; she has no chromosome abnormalities which might have offered an explanation for this anomaly.

Consanguinity of parents was totally absent, which eliminated one support for a diagnosis of recessive disease. In contrast, in Yamanashi, Japan, 12% of the non-environmental cases had some consanguinity of parents, the majority being full cousins.² However, that cultural difference is probably diminishing with a fall in the rate of consanguineous marriage in Japan, once the highest in the world.¹⁰

All but one of the 12 cases of the remarkably common retinal aplasia was sporadic, as would be expected in autosomal recessive disease. The one exception had an elder sister affected, but no counselling was given to the parents after the first child was diagnosed – which also applied to the family of the girl with autosomal recessive retinitis pigmentosa. It is interesting that no cases of retinal aplasia (Leber's congenital amaurosis) were seen in Yamanashi, Japan.²

Many diseases may be difficult for a non-geneticist to attribute to an autosomal recessive cause.⁷ The diagnosis will be very difficult in very rare diseases, as in at least one of the males with macular 'coloboma' (foveal dysplasia) plus retinal aplasia – an affected elder brother makes a recessive cause likely⁸ – and in bilateral non-attachment of retina.¹¹ Indeed there may well be other cases in Table 1 with unsuspected recessive disease, and it is very likely that the catalogue of such diseases in general is still incomplete.

Although bilateral congenital cataract is generally thought to have a good prognosis, there are 12 out of 99 cases in this blind school. The proportion that

Table 4 *Probability of heredity as a cause of blindness*

<i>Likelihood of being hereditary</i>	<i>Auto-somal dominant</i>	<i>Auto-somal recessive</i>	<i>X-linked</i>	<i>Chromosome</i>	<i>Total</i>
++ (Very probable)	7	24	5		36
+ (Probable)	0	12	0	0	12
± (Possible)	0	1	0	1 Down's syndrome 3 deletion in short arm chr 11	5
? (Suspected)	0	5	0	0	5
None	—	—	—	—	40
Subtotal					98
+ 1 Haemolytic disease					1
Total					99

these 12 constitute of all cases of congenital cataract, presumably most coping adequately enough after operation, is unknown. The apparently unrelated systemic diseases in the sporadic cases may be interpreted as suggesting they are not hereditary in origin, although recessive inheritance is possible. There were twice as many males (eight) as females (four), an inexplicable inequality also noted in childhood cataract blindness in 1967.¹² The proportion of cases of blindness due to congenital cataract was even higher in Yamanashi (16/67) than in Edinburgh (12/99), the latter figure being very similar to that for England in the age group 5-15 in 1969-76.¹³

In general, males (65) considerably outnumber females (34), yet only five cases have X-linked recessive disease (of which one is actually a female). The female:male ratio, in the very probably and probably hereditary group, excluding the five cases with X-linked disease was, very surprisingly, 19:27. Perhaps even more surprising was the ratio in the definitely non-hereditary group, namely 11:29. In the Yamanashi Blind School survey a similar under-representation of females compared with males was found both in the hereditary group (12 F to 21 M in the dominant and (very) probably autosomal recessive) and the non-hereditary group (5 F to 13 M). Overall in Japan there were 20 F to 28 M in the ≤ 18 years age group, which excludes the 3 F and 16 M in the ≥ 19 years group, in whom 'retraining' may have been more favoured by, or for, males. The 5 F:7 M ratio in our retinal aplasia cases may easily be due to chance or to lack of differentiation within a heterogeneous group. The 2 F:9 M ratio in retinopathy of prematurity is difficult to explain. Neither Sorsby's statistics¹⁴ nor those of Fraser and Friedmann¹⁵ show a male excess in retrolental fibroplasia as it was then called, but two other reports have recorded a preponderance of males,^{16,17} attributed to their greater immaturity than girls for a given birthweight.

In the group with low birthweight (< 2.5 kg) and low IQ there is a preponderance of males, 3 F to 12 M, but in the small group with a low birthweight but normal IQ there is no significant difference, 4 F to 3 M (Table 3). An excess of males is also seen in those with normal IQ and normal birthweight, 19 F to 29 M, and even more so in those with low IQ and normal birthweight, 7 F to 16 M. In six children, 1 F and 5 M, the birthweight was not known; 4 M had low IQ, and 1 F and 1 M were mentally normal.

The excess of males is difficult to understand. More male babies destined to be blind may survive for some reason. However, the parents of male blind children may feel that these boys should have every educational advantage available, even if this means residential schooling far from home. They may prefer

to keep blind girls at home, regarding them as ineducable, or send them to homes for the multiply handicapped, perhaps feeling that education may not be so important for them and also perhaps being unwilling to allow their daughters to live away from home at an early age. Table 3 shows that the excess of males is marked in the low IQ group, which is consistent with these explanations.

The much greater apparent prevalence of optic atrophy (38% of blind males and the same proportion of blind females) aged 5-15 in England 1969-76¹³ than in our series (15/99) and in the Japanese series (1/67) may be at least in part due to the use of that diagnosis as a broader category in the English series.¹³ Indeed, optic atrophy is a very imprecise diagnosis.

In Yamanashi 14.5% of the school age children had retinopathy of prematurity. However, the youngest was 11 years old, which may indicate the disappearance in Japan of this disease, which has been described as iatrogenic. Fraser and Friedmann record figures which clearly show the epidemic in England and Wales between 1946 and 1956.¹⁸ Our Table 2 may be interpreted as supporting the view sometimes expressed that the disease in Britain, having almost disappeared around the mid-1970s, has recrudesced in the last decade. This has been explained by a recent trend towards high-technology rescue of ever smaller weight premature babies who would not previously have survived. Evidence in Table 2 may support that. Of those with births between 1966 and 1972, only one weighed *less* than 1000 g, whereas during 1975-80 only one weighed *more* than 1000 g. Similarly, the latter evidence would support a paediatrician's claim that measures to prevent this disease have been successful in premature babies with a weight of 1000 g or more. Our preoccupation with sight, however, should not blind us to the multiple handicaps both in this important subgroup and in all the other pupils. Ophthalmic morbidity from prematurity is presumably more common than frank ophthalmic mortality (that is, blindness), so that blindness statistics underestimate the penalty from prematurity. Furthermore, prematurity is a cause of many non-ocular defects in the visual system (Table 1) and of course in many other systems.

Ophthalmologists, having chosen a specialty which absolves them almost entirely from dealing with the problems of general disabling chronic disease and dysthanasia²¹ (unpleasant or painful death, compare euthanasia), may be oversensitive to the multiple handicaps in some unfortunate patients. Paediatricians (and geriatricians, among others) have chosen specialties which demand involvement with patients on many difficult risk-taking occasions, including resuscitation and survival. Vicarious responsibility

by parents (or other relatives) and doctors for decision making on behalf of premature and predictably multihandicapped, mentally retarded, sightless, and insightless babies (or others) has attracted more critical discussion recently.^{19,20}

There were three victims of injury euphemistically called non-accidental, all being mentally retarded. No such diagnoses were made in the Yamanashi Japan, survey.²

Scotland produced only one case in which high myopia may have been a contributory factor (the female probable carrier of X-linked retinitis pigmentosa), whereas 5/67 were found in Yamanashi.² It is surprising that one case of Behçet's disease, with a very well justified diagnosis, was found in Scotland. Only one was also found in Yamanashi Blind School, but the disease is far more prevalent in Japan – 10/100 000 compared with 0.6/100 000 in Britain.²²

The staff at the Royal Blind School have a clear impression of an increase in multiple handicap among the pupils, but that may well result from a reduction in the prevalence of 'pure' blindness, so that more places are available for the multiply handicapped who previously had to go to other institutions. As in Yamanashi, Japan, we have been impressed by the happy atmosphere among the pupils in the Blind School and the very high standard of care and education provided by the very concerned teachers and other staff. The staff:pupil ratio is necessarily high. Their very sheltered environment and the sharing of their affliction with many blind peers help the blind children to minimise their great misfortune, albeit at high economic cost. It is probably easier to become reconciled to blindness or other handicap starting from birth or early childhood than to later blindness. However, at the end of their school days, their problems increase considerably, as they compete in the sighted world for training and employment. We may be guilty of overvaluing sight, as sighted individuals with a professional concern with alleviating defects in vision. The information we provide on hereditary risks (we never volunteer advice) in our ophthalmic genetics clinic probably has less effect than we originally hoped and expected, but does probably make some contribution to the prevention of blindness, often of a lifetime's duration.

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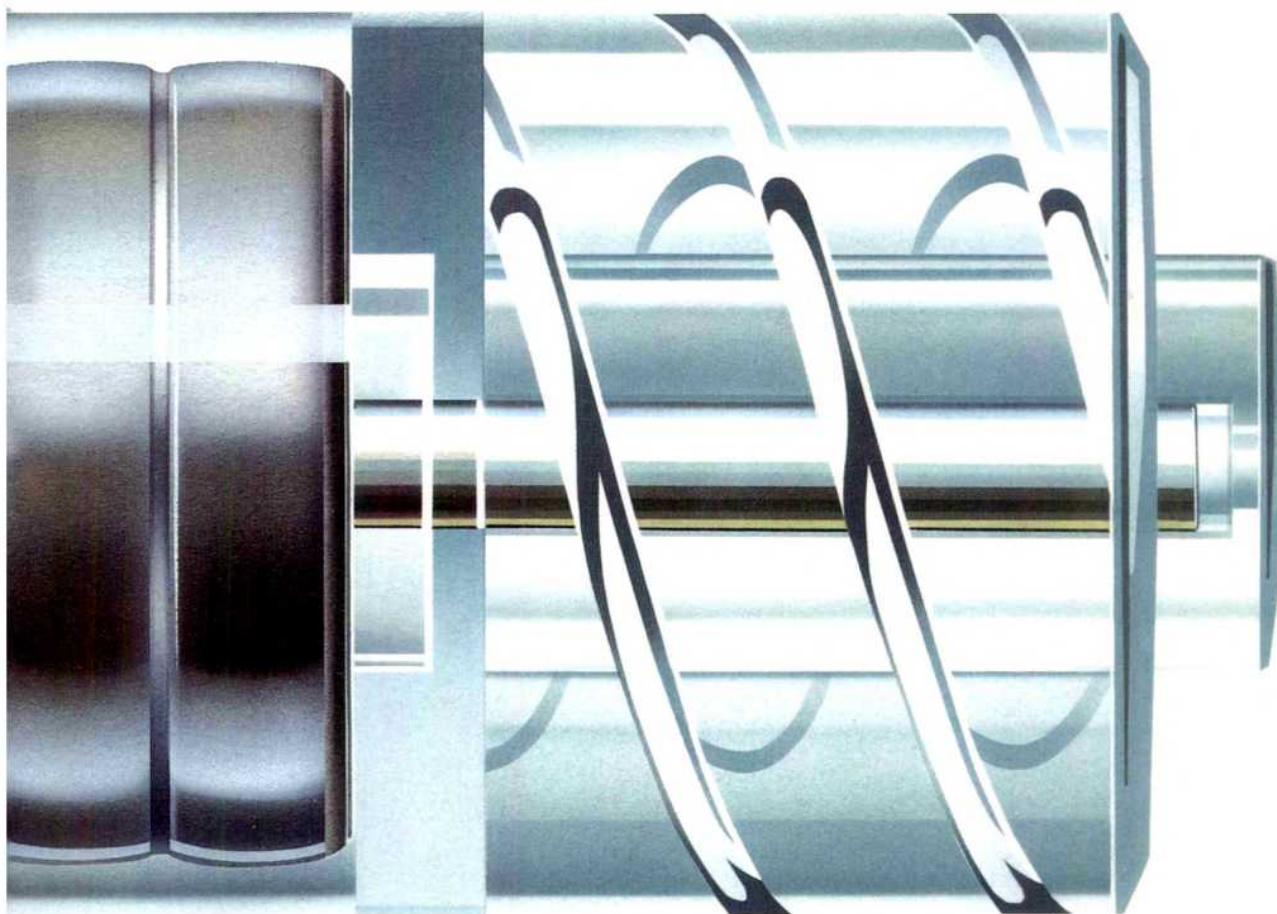
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Experimental posterior uveitis I: A clinical, angiographic, and pathological study

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SUMMARY The clinical, angiographic, and histopathological features of experimental posterior uveitis in the black hooded Lister rat are described. This mild form of experimental allergic uveoretinitis (EAU) is induced by sensitisation with retinal S antigen in Freund's complete adjuvant, and the inflammation produced is confined to the posterior segment of the eye. This allows for the first time precise photographic and angiographic documentation of the evolution of clinical signs, because there is minimal clouding of the vitreous by inflammatory cells. Clinically the disease is characterised by the appearance of disc oedema and periphlebitis, followed by focal infiltrates in the deep retinal layers, with eventual atrophy of the pigment epithelium. Histologically, retinal vasculitis is associated with focal mononuclear cell infiltration and necrosis of the photoreceptor layers. This model closely resembles the clinical features of idiopathic retinal vasculitis seen in man.

Retinal vasculitis is a well recognised syndrome in man that may complicate systemic diseases such as sarcoidosis and Behçet's disease or occur on its own, and it causes a significant visual morbidity in young people.¹ However, its underlying aetiology and pathogenesis are poorly understood, mainly owing to a lack of suitable pathological material. Models developed in primates^{2,3} have shown similarities to posterior uveitis in man, while those in the rabbit^{4,5} and guinea pig⁶ produce an inflammation largely confined to the choroid, because these animals lack a fully developed retinal vasculature. The most widely used laboratory animal is the albino Lewis rat,^{7,8} which, because of its inbred nature and susceptibility to disease, has become an appropriate model for the assessment of uveitogenicity of compounds and for studies of therapeutic prevention.⁹ Immunological studies strongly support the concept that experimental allergic uveoretinitis (EAU) is a specific antiretinal autoimmune phenomenon predominantly mediated by T lymphocytes.¹⁰ In the Lewis rat, however, certain clinical features such as disc

oedema and periphlebitis may be inferred from pathological studies, but direct observation of the evolution of these signs is impossible because of clouding of the ocular media by inflammatory cells. Rapid destruction of the photoreceptor layer prevents the study of early events that may be important in initiating disease, and the regression of disease within one week does not allow time for pharmacological intervention.

In pilot experiments we observed that EAU in the black hooded Lister rat induced by retinal S antigen (S-ag) in Freund's complete adjuvant (FCA) produced a form of EAU that predominantly affected the retina, so that recording the evolution of clinical signs was possible. In this paper we present the clinical, angiographic, and pathological features of this disease in a series of 36 rats. In a subsequent paper the electroretinographic findings will be discussed.

Materials and methods

Animals. In all studies male black hooded Lister rats (Bantin and Kingman) weighing 250-300 g were used.

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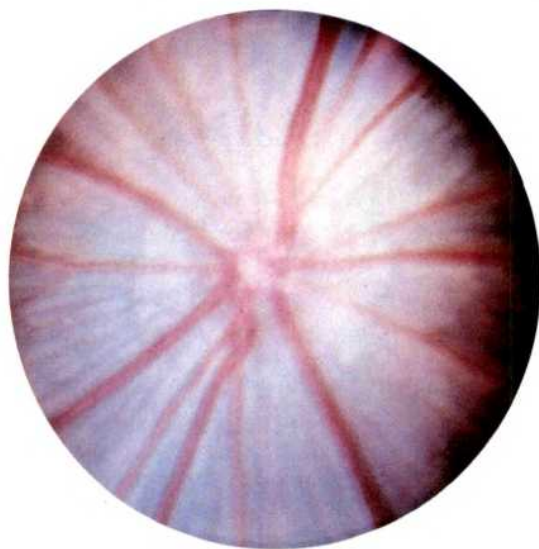


Fig. 1a

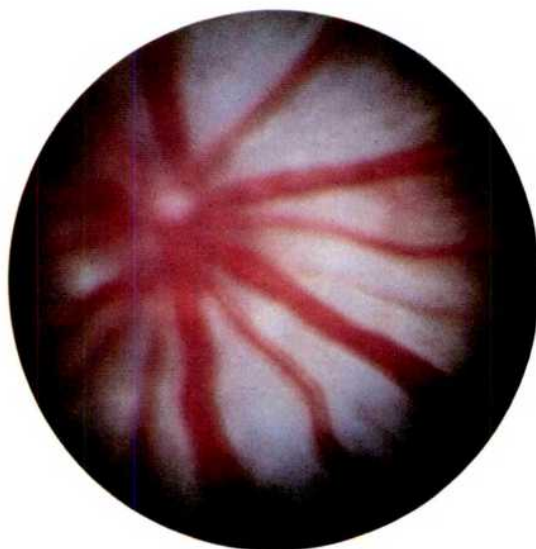


Fig. 1b

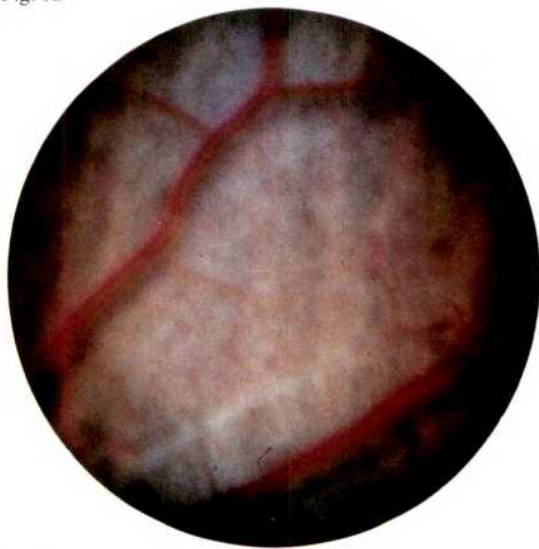


Fig. 1c



Fig. 1d

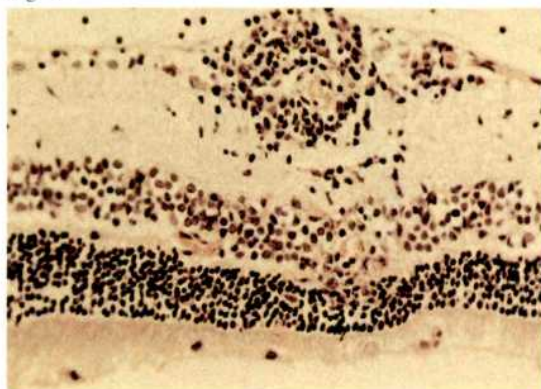


Fig. 1e

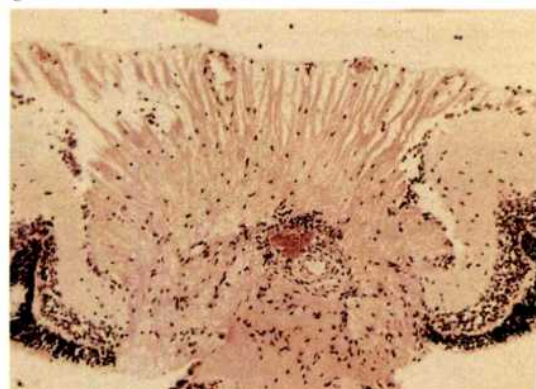


Fig. 1f

Inoculation protocol. In all experiments animals were injected with purified porcine retinal S antigen. Details of the purification procedure are published elsewhere,¹¹ but in brief this was carried out by extraction from fresh retinas in low ionic strength buffer, ammonium sulphate precipitation, and then purification by size fractionation on Ultrogel AcA34 followed by hydrophobic absorption chromatography on phenyl-sepharose (Pharmacia). The final purity of the injected antigen was 80% as determined by sodium dodecyl sulphate polyacrylamide gel (SDS-PAGE) electrophoresis and scanning densitometry. The S antigen in phosphate buffered saline (PBS) was emulsified in Freund's complete adjuvant enriched with *Mycobacterium tuberculosis* 3 mg/ml (Ministry of Agriculture and Fisheries, Weybridge, England). Each animal received 0.1 ml per hind footpad to a final dose of 50 µg S antigen per animal. Control animals were injected in the same manner with PBS/FCA.

Clinical assessment. Each animal was observed on a daily basis from day 10 after inoculation. The pupil was dilated with a drop of tropicamide hydrochloride 1%, and disease activity was assessed by slit-lamp biomicroscopy and fundus photography (Zeiss fundus camera). Where detailed fundus examination was required, the animals were anaesthetised with a single intraperitoneal injection of ketamine hydrochloride (Ketalar) 120–180 mg/kg, which provided a suitable level of anaesthesia for 20 minutes. Serial photographs were taken to record the evolution of clinical signs. Where particular features were noted, or at the termination of the experiment, animals were anaesthetised with intraperitoneal urethane (1.5 g/kg), and fluorescein angiography was carried out.

Fluorescein angiography. The tail vein of the anaesthetised animal was cannulated with a 25 gauge butterfly needle (Abbott Ireland Ltd) that had been heparinised to ensure patency. In some cases the hypotensive effect of the anaesthetic was such that the tail vein could not be cannulated, and in these animals a cannula was introduced into the deep femoral vein via a flank incision. 0.1 ml of 5% sodium fluorescein was injected and a fluorescein angiogram recorded with the Zeiss fundus camera and Ilford FP4 film using the appropriate filters. For peripheral views of the retina the head of the animal was rotated

manually. The angiogram was terminated at five minutes. The animals were then killed after cardiac puncture and the eyes removed for histological processing.

Histology. Fresh eyes removed from the animals were placed in 4% glutaraldehyde (EM grade, Emscope Laboratories) for 10 minutes. The globe was then incised with a razor blade to allow access of the fixative to both anterior and posterior chambers and remained in glutaraldehyde for a further 12 hours before being trimmed and placed in 10% neutral buffered formalin. Elimination of this step resulted in a high incidence of artefactual retinal detachment. The eyes were dehydrated in graded alcohols, cleared in toluene, and embedded in paraffin for sectioning. Haematoxylin and eosin staining was used throughout.

Antibody studies. All animals used in this study were bled weekly under ether anaesthesia. Antibodies against S antigen (S-ag) were detected by means of a modified radiometric plate binding assay as described elsewhere.¹² Briefly, polystyrene microtitre plates (Dynatek) were coated with porcine S-ag 5 µg/ml in PBS for two hours at 37°C. The plates were washed in PBS and then incubated with 0.4% bovine serum albumin (BSA) in PBS for two hours at room temperature. Sera from the animals were diluted (1/4 to 1/256) in PBS/BSA and incubated on the plate (1 hour 37°C, 1 hour 4°C) and washed. Fixed antibodies were detected with ¹²⁵I protein A (Pharmacia) diluted to approximately 1:100 in radioimmunoassay diluent (0.4% BSA in PBS and 0.05% Tween (polysorbate) depending on the specific activity. The plates were then incubated (1 hour 37°C, 1 hour 4°C), washed, and counted in a gamma counter (Compugamma). The antibody titre was expressed as a reciprocal of the dilution that gave half the maximum counts.

Results

Immunisation of black hooded Lister rats with retinal S antigen produced a retinal vasculitis in 90% of the animals observed. The onset of disease, defined by the appearance of vitreous cells and tortuous retinal vessels, varied from 14 to 57 days. The duration of disease, defined as the time from onset until the disappearance of vitreous cells and regression of disc

Fig. 1 Colour photographs of the rat fundus. (a) Normal rat optic disc. (b) Diseased disc at day 18 after inoculation showing massive swelling, thickening, and tortuosity of retinal vessels and loss of the normal nerve fibre layer reflex. There is a slight haze due to vitreous cells. (c) Normal rat retinal periphery. (d) Disease in the periphery showing retinal exudates surrounding the capillaries, vascular engorgement with some sludging of blood, and intraretinal haemorrhages. (e) Photomicrograph of diseased rat retina showing a perivasculitis composed mainly of lymphocytes and a small mononuclear cell infiltrate in the photoreceptor layer (haematoxylin and eosin). (f) Photomicrograph of diseased rat optic disc in oblique section showing swelling, vasculitis of central vessels, predominantly the vein, and some peripapillary retinal folds (H and E). Figs. 1a–d, $\times 44$. Figs. 1e,f, $\times 200$.

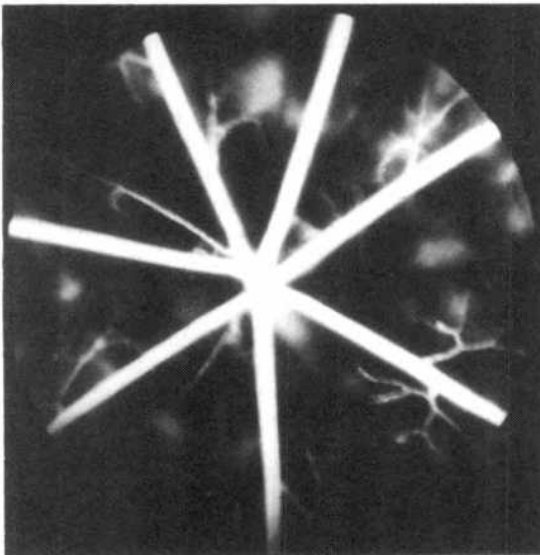


Fig. 2a

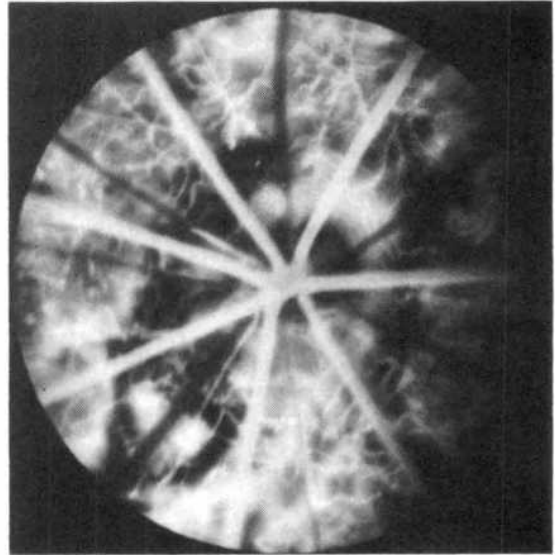


Fig. 2b

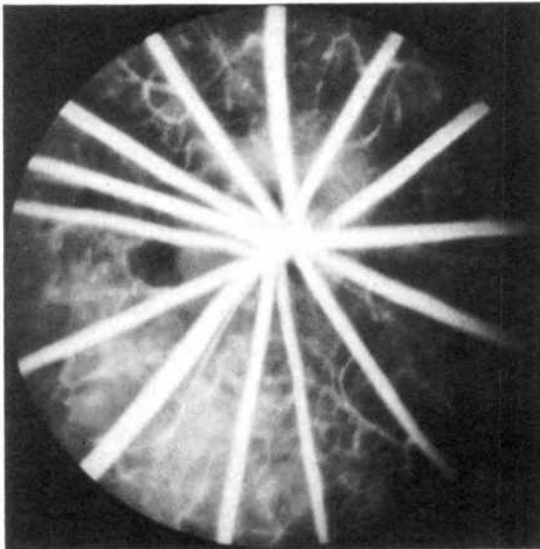


Fig. 2c

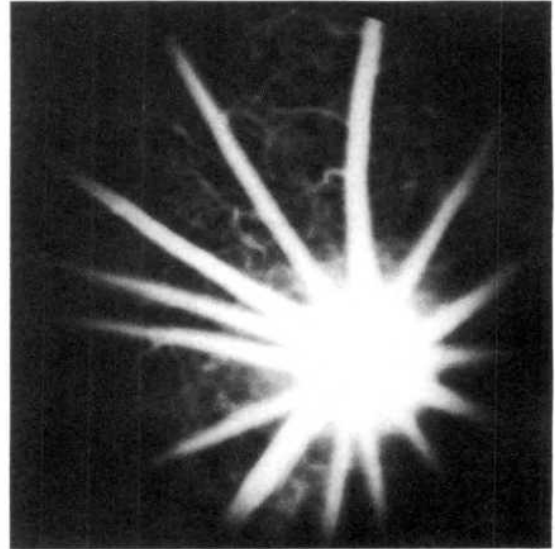


Fig. 2d

Fig. 2 Fluorescein angiogram of a normal rat retina showing (a) early arterial, (b) early venous (c) late venous, and (d) late stages of the angiogram.

oedema and tortuous vessels, ranged from 5 to 23 days (Table 1). The disease did not recur in any animal for at least three months as judged by these criteria.

CLINICAL COURSE

The disease could be divided into early, intermediate, and late stages. The appearances of a normal rat retina are shown in Figs. 1a and 1c. There

is a small hyaloid remnant on the disc which is common to most rat eyes. The retinal vessels are generally straight and there is a well defined nerve fibre layer.

The early stage of the disease was defined by dilation and tortuosity of the retinal vessels (veins more than arteries) and the appearance of a few cells in the vitreous. One to two days after this the optic disc became swollen, the definition of the nerve fibre

Table 1 Time of onset and duration of disease

	Experimental animals	Controls
No. developing disease	32/36 (90%)	0/15
Disease onset	14 to 57 days (25.1 ± 12.4)	0
Disease duration	5 to 23 days (12 ± 5.6)	0

Figures in brackets are the mean $\pm$ SD.

layer was lost, and small intraretinal infiltrates appeared.

The intermediate stage showed the maximum number of clinical signs. Figs. 1b and 1d show a retina at this stage 18 days after inoculation. This stage lasted from seven to 10 days.

In the late stage of disease the optic disc and peripapillary area returned to normal, the vessels regained their normal calibre, and vitreous cells disappeared. In the periphery the exudates faded but pigment epithelial atrophy remained in these areas. Significant anterior uveitis, cataract formation, and the development of posterior synechiae did not develop in any animal. Control animals showed no evidence of vitreous cells, and the fundus remained normal throughout.

FLUORESCIN ANGIOGRAPHY

Fluorescein angiograms were performed to characterise the early, intermediate, and late stages of disease and at the end of observation. A normal rat fluorescein angiogram is shown in Figs. 2a, b, c, d. In the late phase of the angiogram there was a small amount of leakage of dye from the disc in control animals.

In the early stage of disease leakage of dye was evident at the disc and in peripheral areas associated with intraretinal infiltrates. In the intermediate stage (Figs. 3a, b, c) marked thickening and tortuosity of vessels at the disc was evident in the early phase, with extensive leakage of dye in the late phase. In the periphery there was early leakage of dye, which persisted into the late films. Even when the disc had returned to normal clinically, there was persistent leakage of dye, though this became less with time. Areas of peripheral pigment epithelial atrophy showed staining but no leakage at four months.

HISTOLOGY

Anterior segment (all stages of disease). A mild mononuclear cell infiltrate was observed in the anterior chamber in some animals at the height of the intermediate stage. Infiltration of the vitreous round the ciliary body was seen but was always small and reflected changes occurring in the vitreous as a whole. Histological evidence of posterior synechiae were not seen.

Posterior segment (early stage). The earliest histological feature noted was leakage of inflammatory cells from the disc accompanying a mild vasculitis of central disc vessels. This was followed by a pan-vasculitis affecting the superficial retinal vessels (Fig. 4b), the veins being more affected than the arteries. At this stage mononuclear cells containing pigment were observed singly in areas of the photoreceptor layer (Fig. 1e). The appearance of these cells was associated with pigment epithelial thinning, but whether these cells were derived from blood borne monocytes that had acquired pigment during their passage through the RPE, or whether they were transformed pigment epithelial cells could not be ascertained.

Posterior segment (intermediate stage). The intermediate stage was characterised by swelling of the optic disc due to oedema (Fig. 1f) with increasing numbers of inflammatory cells in the vitreous and a pan-vasculitis (Figs. 4a, b). In the retina itself mononuclear cell infiltrates were observed, which formed clusters in the photoreceptor layer causing retinal folds, and in all cases were associated with focal photoreceptor necrosis. The retinal pigment epithelium (RPE) always remained intact, and the choroid was thickened in only the severest cases.

Posterior segment (late stage). In this stage the optic disc returned to normal. The retinal vessels appeared normal but in the photoreceptor layers areas of focal necrosis were superseded by fibrous replacement with concomitant loss of the outer nuclear and plexiform layers. In severe cases there was also reduction in the thickness of the inner nuclear layer, probably due to transsynaptic degeneration.

Antiretinal S antigen antibody titres. The antibody levels against S antigen as determined by the plate binding assay are shown in Fig. 5. The titres were highest in the third week and remained raised for some time afterwards. Correlation between antibody titres and clinical or pathological disease was not evident in individual animals.

Discussion

Since the original work of Elschnig¹² and Woods,¹³ which implied that some forms of uveitis were autoreactive, considerable advances have been made in refining animal models of human uveitis. There are no models that exactly mirror the clinical variety of disease in man, but all have increased our knowledge by correlation of clinical signs with underlying pathological events. The production of EAU, which has been produced by the injection of whole retinas, retinal extracts, and rod outer segments,^{14,15} may now be elicited by a single minute dose of highly purified

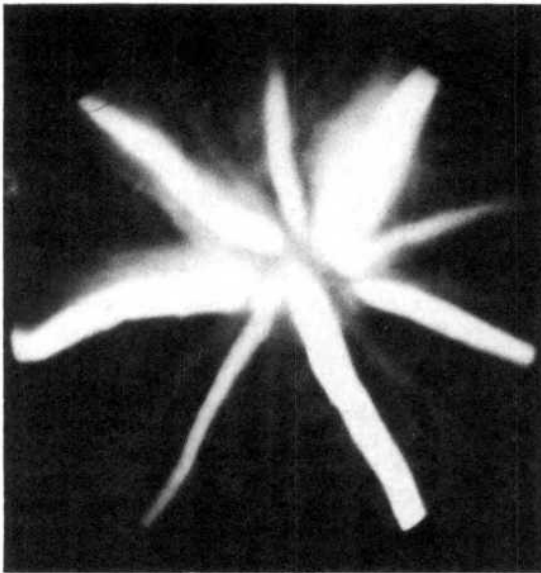


Fig. 3a

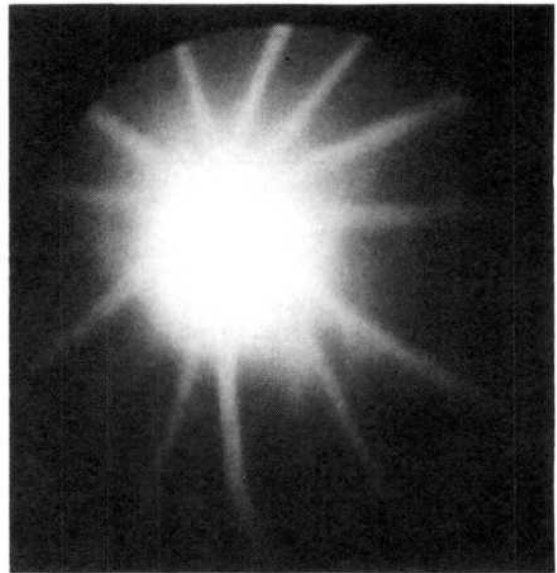


Fig. 3b

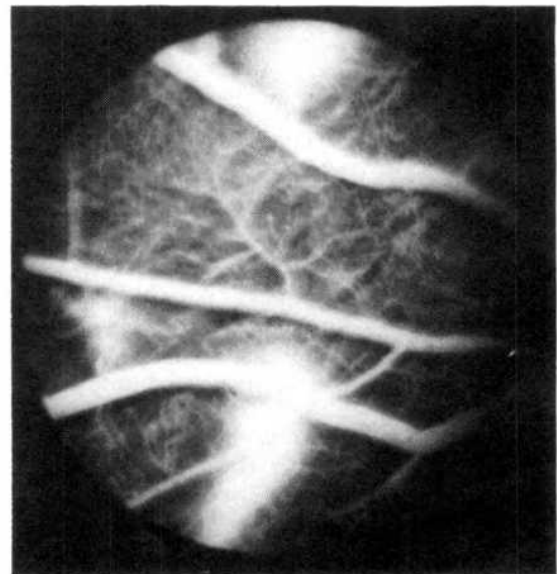


Fig. 3c

Fig. 3 Fluorescein angiogram of a rat with disease 16 days after inoculation: (a) early arterial phase shows marked thickening and tortuosity of vessels, (b) late phase of disc shows marked leakage of dye, and (c) peripheral view shows leakage of dye from inflamed retinal vessels.

material from the retina, one of which is retinal S antigen. Other purified antigens, notably rhodopsin and interphotoreceptor binding protein (IBRP), have also been shown to produce disease.^{16,17} The nature of the inflammation produced and the extent to which it affects various parts of the eye are dependent on the amount of antigen given,¹⁸ the adjuvants given with it,⁷ the species from which the antigen is derived—whether homologous or hetero-

logous—and the species and strain of the experimental model,^{19,20} the latter depending largely on the animal's vascular architecture. Correlation between disease and the purity of the administered antigen has not yet been reported. The disease in the rat may thus vary from an acute necrotising panophthalmitis, with involvement of the anterior segment in genetically susceptible Lewis rats, to a mild focal uveoretinitis in genetically resistant pigmented animals.^{19,20}

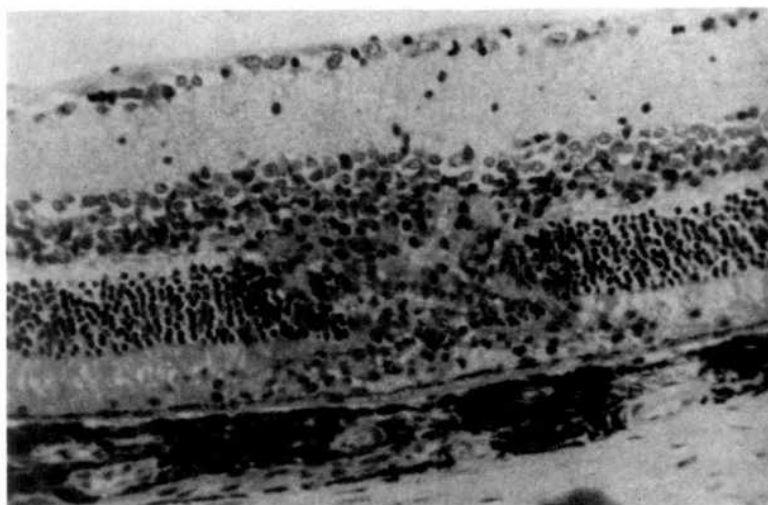


Fig. 4a

Fig. 4 (a) Photomicrograph of diseased rat retina showing a focal mononuclear cell infiltrate in the photoreceptor, outer nuclear, and plexiform layers. The pigment epithelium appears intact and there is no choroidal involvement (H and E). (b) Photomicrograph of diseased retina in the early stage of disease showing perivascularitis of the retinal vessels as an early sign. The photoreceptor layer appears normal. The retina is artefactually detached (H and E). $\times 300$.

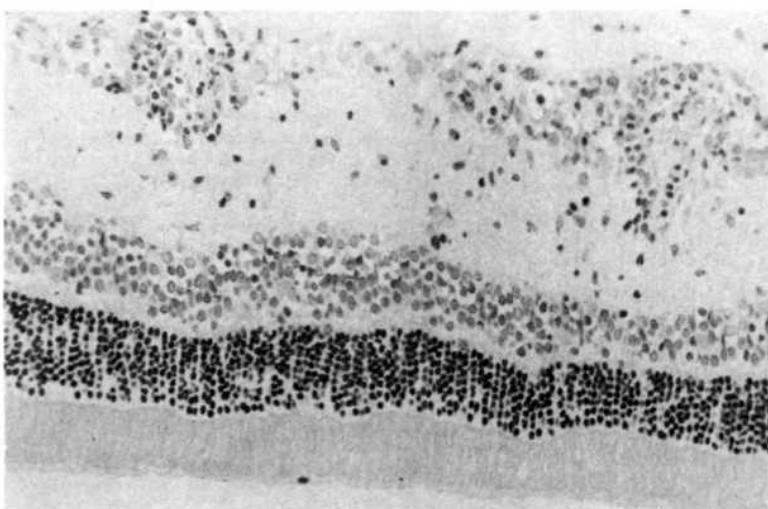


Fig. 4b

In this study we have documented the clinical, angiographic, and histological features of EAU in the black hooded Lister rat. The disease in this animal is variable in both its time of onset and duration, and some animals did not develop disease over a period of four months' continuous observation. However, this inconsistency has several practical advantages. The slowness of onset of disease, in some cases taking more than one week from the initial changes to full development of clinical signs, allows early histopathological events to be studied in greater depth, particularly with regard to the anatomical site of early lesions. The duration of disease, though again variable, is more prolonged than in albino animals, and

this is relevant when considering the design of regimens for therapeutic intervention. The clinical features such as disc swelling and retinal infiltrates around blood vessels, with accompanying fluorescein leakage, are strikingly similar to those found in man, though we did not find any evidence of occlusive vasculitis as seen in Behçet's disease.

Pathologically, inflammation in this animal is almost entirely confined to the retina, with only minimal focal involvement of the choroid in animals with very severe disease. This is in contrast to practically all other animal models. Actual destruction of the photoreceptors was associated with a mononuclear cell infiltrate, which has also been

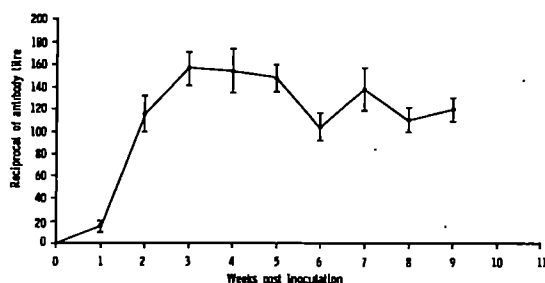


Fig. 5 Graph showing the relationship between antiretinal S-antigen antibody titres and time after inoculation. Controls are not shown as no rise in titre was observed.

observed by other authors,⁶ but the origin of these cells remain uncertain. They may be derived from monocytes in the blood gaining access from damaged retinal vessels or through an inflamed pigment epithelium, or possibly they may be transformed retinal pigment epithelial cells, though the latter seems less likely. In the majority of cases, after the disease has run its course, viable photoreceptors remain in the absence of any active inflammation. This has been observed in few other models and raises the possibility of inducing recurrent uveitis by further immunological attacks on this antigenic target.

These experimental animals produce antiretinal antibodies as shown by the plate binding assay and indirect immunofluorescence on cryostat sections of rat retinal tissue (data not shown). The initial rise in antibody titre is presumably directed against the immunising antigen, with the levels being maintained by the depot effect of the adjuvant. We could find no evidence of a correlation between disease activity and antibody levels, a finding that confirms the work of other authors and is similar to that found with uveitis in man.²¹

The present model of retinal vasculitis in the black hooded Lister rat is a useful addition to the other models of retinal S antigen induced disease. Direct observation of the clinical and angiographic features of this slowly evolving disease will promote our understanding of the mechanisms underlying posterior uveitis in animals, with important clinical and therapeutic implications for the study of this disease in man.

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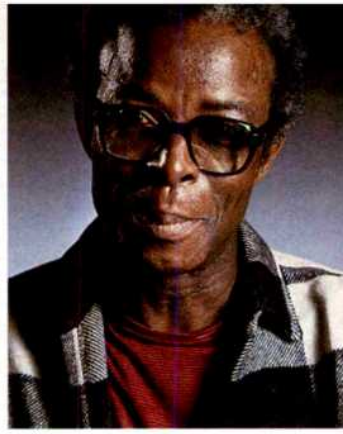
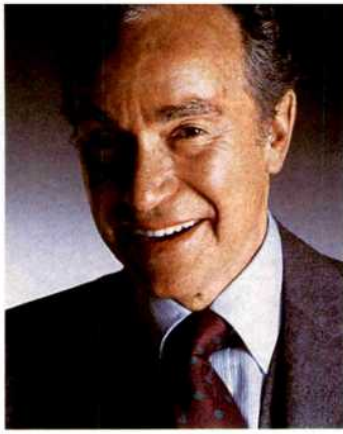
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Epithelial metabolism of the corneal graft is abnormal

ANTTI VANNAS,¹ BRIEN A HOLDEN,² AND DEBORAH F SWEENEY²

From the ¹University Eye Clinic, Helsinki, Finland, and the ²Cornea and Contact Lens Research Unit, School of Optometry, University of New South Wales, Australia

SUMMARY Both eyes of 16 patients who had undergone unilateral penetrating keratoplasty were examined in this study. The mean corneal oxygen uptake rate in the centre of the graft was 3.88 (SD 0.55) mmHg/s and in the control eye was 4.29 (SD 0.62) mmHg/s. In the temporal host periphery the results for the grafted and control eyes were 4.52 (SD 0.54) mmHg/s and 4.26 (SD 0.52) mmHg/s respectively. The differences in the oxygen uptake rate between the centre of the graft cornea and the contralateral control eye and between the centre and periphery of the graft eye were statistically significant ($p < 0.01$). The central corneal touch threshold of the graft eye showed good recovery in four patients, while the remaining 12 had no or minimal recovery. The central and temporal epithelial and corneal thicknesses of the graft and the control eyes were not significantly different. The central endothelial cell density was 1383 cells/mm² in the graft and 3053 cells/mm² in the control eye. As corneal oxygen uptake reflects changes in aerobic epithelial metabolism, it is possible that there is a link between loss of neural integrity of graft epithelium and lowered epithelial aerobic metabolism following penetrating keratoplasty.

The cornea of the aphakic eye swells less with a hypoxic stimulus than does the cornea of the paired normal eye.¹⁻³ However, neither the removal of the crystalline lens nor the endothelial changes produced by surgery appear to be related to the difference in hypoxic corneal swelling response. Rather, the difference has been attributed to the lower aerobic metabolic activity of the epithelium due to partial denervation of the cornea following surgery.⁴

Differences in epithelial aerobic metabolism are reflected in the corneal oxygen uptake rate when corneal thickness, the main factor influencing diffusion of oxygen, remains approximately the same.⁵

The present study was initiated to investigate further the effects of denervation on aerobic metabolic activity. Both the central and peripheral corneal oxygen uptake rates and sensitivities in both eyes of 16 patients with unilateral penetrating keratoplasty were measured.

Materials and methods

SUBJECTS

Sixteen subjects who had undergone unilateral penetrating keratoplasty participated in the study after

their informed consent was obtained. The patient characteristics and details of the surgery are listed in Table 1. The average age of the patients was 43 years (range 24-60 years) and the time after surgery averaged 29 months (range 10-102 months). All the

Table 1 Details of subjects

Subject	Sex	Age	Operated eye	Reason for surgery	Time since surgery (months)
1	M	28	R	K	10
2	M	54	R	H	10
3	F	39	L	S	13
4	M	60	L	H	14
5	F	54	R	K	15
6	M	36	L	K	21
7	F	56	R	S	22
8	M	38	L	K	24
9	M	44	L	K	24
10	F	39	R	K	27
11	M	24	L	K	28
12	M	47	R	K	32
13	M	29	R	K	36
14	M	33	L	H	38
15	F	47	L	K	52
16	M	60	L	B	102
Mean		43			29
SD		12			22

K=Keratoconus. H=Herpes simplex. S=Past corneal trauma. B=Bullous keratopathy.

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operations were performed by the one surgeon using the same technique. The diameter of the grafts was 8 mm. The running 10-0 nylon suture was removed after six months. Local corticosteroid therapy was also stopped at this time. Inflammatory changes were not observed in any of the corneas at the time of measurement.

METHODS

Corneal oxygen uptake rate. Corneal oxygen uptake rate was measured with a polarographic oxygen sensor^{6,7} applied directly to the anterior cornea. The oxygen sensor (Radiometer E5057/0, 8 mm in diameter with a 25 μ m diameter cathode) was covered with a 12.5 μ m thick polypropylene membrane. The sensor current was amplified by a radio-meter amplifier (PHM 73) linked to a microcomputer (Apple II Plus). The sensor was calibrated periodically at 34°C in air (155 mmHg PO₂) and nitrogen-saturated water (0 mmHg PO₂) baths. The corneal oxygen uptake rate was determined by recording the time required for the oxygen tension at the membrane to drop from 140 to 100 mmHg. The result is expressed in mmHg/s.

Three readings of the central and the temporal peripheral corneal oxygen uptake rate of each eye were taken. The average variability (SD) for three readings taken at each measurement session was 0.22 mmHg/s.

Corneal touch threshold. Corneal sensitivity was measured with a Cochet-Bonnet aesthesiometer,

which consists of a 0.12 mm diameter nylon monofilament encased in a cylinder. The aesthesiometer was mounted on a triaxis holder so that its position and movement could be controlled in the x, y, and z meridians in an arrangement similar to that used by Millodot.⁸ The length of the monofilament can be varied from 6.0 to 0.5 cm. This range corresponds to pressures of 1 to 20 g/mm² (cross-sectional area of the filament, 0.0113 mm²). To obtain a measurement the aesthesiometer was moved slowly toward the cornea at a constant velocity until visible bending of the filament occurred. The subject was asked to tap on the table if touch was felt. Presence or absence of the blink reflex was also noted. The aesthesiometer was first set at a maximum thread length of 6.0 cm and the length was then decreased by 0.5 cm increments until the patient felt three of the six stimuli. This filament length was recorded as the value corresponding to the corneal touch threshold. The central and temporal regions of the graft and control corneas were measured.

Epithelial thickness. The Payor-Holden micro-pachometer, consisting of a Haag-Streit pachometer adapted to a Rodenstock Model 2000 biomicroscope, was used to monitor central and temporal epithelial thickness. The design and operation of the system have been previously described.⁸ Ten readings of central and temporal epithelial thickness were obtained; the average standard deviation for the 10 readings was 5 μ m (10% of epithelial thickness).

Corneal thickness. Total corneal thickness was measured centrally and temporally with the micro-

Table 2 Central and temporal corneal characteristics of the graft patients

Subject	Oxygen uptake rate (mmHg/s)						Corneal touch threshold (mg/mm ²)					
	Central cornea			Temporal cornea			Central cornea			Temporal cornea		
	Graft	Control	Diff.	Graft	Control	Diff.	Graft	Control	Diff.	Graft	Control	Diff.
1	4.45	5.26	-0.81	4.33	4.35	-0.02	200	11	189	12	11	1
2	3.14	3.55	-0.41	5.01	3.62	1.39	200	11	189	11	11	0
3	4.28	5.09	-0.81	5.23	4.85	0.38	11	11	0	11	11	0
4	4.21	4.25	-0.04	4.70	3.88	0.82	200	11	189	16	11	5
5	3.40	4.48	-1.08	4.17	4.42	-0.25	36	16	20	21	13	8
6	4.14	4.35	-0.21	4.35	4.15	0.20	200	11	189	12	11	1
7	3.23	3.36	-0.13	3.99	3.30	0.69	145	11	134	21	11	10
8	4.03	4.51	-0.48	4.39	4.56	-0.17	200	12	188	11	13	-2
9	4.04	4.64	-0.60	4.33	4.26	0.07	200	11	189	11	11	0
10	4.11	4.48	-0.37	4.21	4.45	-0.24	145	11	134	11	11	0
11	4.39	4.73	-0.34	4.44	4.62	-0.18	200	11	189	11	11	0
12	3.78	3.80	-0.02	4.15	5.17	-1.02	13	11	2	21	11	10
13	2.93	3.01	-0.08	3.77	3.35	0.42	200	11	189	11	13	-2
14	4.51	4.68	-0.17	4.63	4.60	0.03	200	12	188	6	12	-6
15	3.02	3.83	-0.81	6.03	4.09	1.94	11	11	0	11	11	0
16	4.47	4.68	-0.21	4.54	4.54	0.00	200	11	189	21	45	-15
Mean	3.88	4.29	-0.41	4.52	4.26	0.25	148	11	136	14	13	1
SD	0.55	0.62	0.33	0.54	0.52	0.70	80	1	80	5	6	6
t value			4.81			1.38			6.58			0.65
p			0.001			ns			0.001			ns

pachometer. Ten readings of corneal thickness were obtained on each measurement occasion; the average standard deviation for 10 readings was 4 μm (0.8% of corneal thickness).

Endothelial morphology. The central endothelium was photographed with Kodak Tri-X pan film using a non-contact specular microscope as described previously.^{9,10} Fifteen photographs were taken of each eye. The photographs were printed at 13 $\times$ magnification from negatives which contained images of endothelial cells at approximately 30 $\times$ magnification. A precision microscopic grid of known dimensions was photographed at the corneal plane to enable exact quantification of the endothelial mosaic. Five photographs of good quality were chosen from the 15 photographs of each eye. Technicians traced 50 cells from each photograph on to a plastic overlay using a fine black marking pen, giving a total of approximately 250 cells traced per eye. The cell tracings were analysed with an IBAS-2 automatic image analysis system (Kontron, West Germany). This instrument measured individual cell areas (adjusted for the width of the pen lines) and calculated endothelial cell density (ECD) and the coefficient of variation of mean cell size, which was used as an index of endothelial cell polymegathism.

Data analysis. The difference between the two eyes were tested for statistical significance by a *t* test for matched pairs. A 95% confidence level was chosen as the criterion for accepting a difference as being significant.

Results

The corneal characteristics of all the subjects are listed in Table 2. The central corneal oxygen uptake rate of the graft eye (3.88 (SD 0.55) mmHg/s) was significantly depressed in comparison with the contralateral control eye (4.29 (SD 0.62) mmHg/s, $p < 0.001$, Student's two-tailed paired *t* test). In addition, the corneal oxygen uptake rate was depressed in the centre of the graft in comparison with the temporal host periphery (3.88 (SD 0.55) mmHg/s vs 4.52 (SD 0.54) mmHg/s. The mean reduction was 9% and this was also statistically significant (< 0.05 , Student's two-tailed paired *t* test). The difference, however, between the central (4.29 (SD 0.62) mmHg/s) and temporal (4.26 (SD 0.52) mmHg/s) measurements of the control eye (0.7%) was not statistically significant.

Mean corneal touch threshold for all subjects was also significantly reduced in the centre of the graft eye in comparison with the centre of the control eye and with the temporal host periphery ($p < 0.001$, Student's two-tailed paired *t* test).

There was no statistically significant difference in mean epithelial or total thickness between the graft and control central and temporal corneas.

The average central endothelial cell density in the graft eye was 1383 cells/mm² and in the control eye 3053 cells/mm² (Table 3). The difference in the endothelial cell density between the graft and control eyes was 55%. This reduction was statistically significant ($p < 0.001$, Student's two-tailed paired *t* test).

Epithelial thickness (μm)						Corneal thickness (μm)					
Central cornea			Temporal cornea			Central cornea			Temporal cornea		
Graft	Control	Diff.	Graft	Control	Diff.	Graft	Control	Diff.	Graft	Control	Diff.
61	73	-12	40	57	-17	593	555	38	345	608	-263
71	62	9	77	34	43	488	564	-76	663	514	149
57	52	5	90	57	33	590	553	37	688	626	62
50	76	-26	33	72	-39	457	569	-112	395	670	-275
53	47	6	58	52	6	608	427	181	293	550	-257
51	55	-4	50	68	-18	523	500	23	662	590	72
66	68	-2	38	90	-52	526	540	-14	322	661	-339
42	54	-12	76	47	29	508	421	87	663	462	201
59	42	17	55	60	-5	497	455	42	566	571	-5
60	46	14	30	36	-6	547	517	30	616	385	231
71	72	-1	68	67	1	535	496	39	498	645	-147
54	52	2	58	83	-25	580	494	86	594	589	5
48	59	-11	56	47	9	502	460	42	530	415	115
55	69	-14	52	68	-16	468	474	-6	523	633	-110
52	49	3	40	20	20	523	431	92	594	319	275
60	59	1	43	61	-18	544	604	-60	550	695	-145
57	58	-2	54	57	-3	531	504	27	531	558	-27
8	11	11	17	18	26	45	56	71	129	110	197
		0.70			0.45			1.47			0.53
		ns			ns			ns			ns

Table 3 Central endothelial cell density (ECD) and polymegathism

Subject	ECD cells/mm ²			Polymegathism		
	Central cornea			Central cornea		
	Graft	Control	Diff.	Graft	Control	Diff.
1	2237	3799	-1562	0.291	0.243	0.048
2	1031	2747	-1716	0.458	0.263	0.195
3	2531	3524	-993	0.327	0.283	0.044
4	1780	3201	-1421	0.276	0.316	-0.039
5	463	3058	-2595	0.280	0.247	0.033
6	1091	3499	-2408	0.312	0.285	0.036
7	1443	1788	-345	0.303	0.286	0.017
8	1402	3084	-1682	0.356	0.319	0.037
9	1173	2834	-1661	0.295	0.319	-0.024
10	2085	2792	-707	0.276	0.271	-0.002
11	1679	4095	-2416	0.344	0.280	0.065
12	1122	3348	-2226	0.298	0.275	0.024
13	1162	3268	-2106	0.321	0.229	0.092
14	1176	3571	-2395	0.257	0.312	-0.054
15	782	2892	-2110	0.221	0.295	-0.074
16	973	1354	-381	0.301	0.333	-0.031
Mean	1383	3053	-1670	0.307	0.285	0.011
SD	552	693	733	0.052	0.030	0.121
t value			8.83			0.35
P			0.001			NS

There was no statistically significant difference in the endothelial polymegathism of the graft and control eyes.

Discussion

The results of this study show that the corneal oxygen consumption of the graft epithelium is not only significantly lower than the normal contralateral cornea but also lower than the host periphery. The periphery of the host cornea was subjected to the same post surgical conditions as the graft, yet retained normal oxygen uptake characteristics. This suggests that the depressed oxygen uptake of the graft is not due to postsurgical treatment such as steroids. As differences in corneal oxygen uptake rates are primarily caused by differences in epithelial metabolic activity,⁵ these results indicate that the epithelial metabolic activity of the graft cornea is depressed despite the long postoperative period. Even in the same eye the epithelium at the centre and periphery has different levels of metabolic activity following penetrating keratoplasty. This reduction, however, does not influence epithelial thickness, as measurements were similar in the graft and control eyes.

After penetrating keratoplasty the properties of the graft cornea are altered. Bourne and Brubaker¹¹ showed that endothelial permeability to fluorescein is reduced with reduced endothelial cell density. This study showed a marked reduction of the endothelial

cell density in the graft eye. Similar findings have been reported by others.¹²⁻¹⁶ A relevant question is whether endothelial changes influence corneal oxygen uptake rate. In our patients corneal oxygen uptake differences did not correlate with endothelial cell loss (Pearson correlation, $r=0.14$, $p=0.60$). This finding is not unexpected, as calculations with a computer model¹⁷ show that a two-fold increase or decrease in endothelial oxygen consumption has no significant effect on the uptake rate.¹⁸

There was no statistically significant difference between the mean central cornea thickness of the graft and control eyes. However, in individual cases, the thickness of the graft and control eye did vary (Table 2). As reported previously, significant differences in corneal thickness can alter the rate of passive diffusion of oxygen from the atmosphere to the aqueous humour.⁵ To test whether this may have influenced our findings we used the technique described by Holden *et al.*⁵ to recalculate the oxygen uptake rates to allow for this difference. After recalculation the differences between the graft and control eye central oxygen uptake rates and between the central and peripheral oxygen uptake rates of the graft cornea were still statistically significant. Thus the overall results were not influenced by corneal thickness changes in individual cases.

Problems with neovascularisation, punctate epithelial lesions, and infections with extended contact lens wear following keratoplasty have been reported.^{19,20} Epithelium with a lower than normal aerobic metabolism must be regarded as compromised and as a result may be more prone to develop infections during contact lens wear.^{19,21} The compromised epithelium could also be more prone to secrete neovascularogenic substances²² causing superficial neovascularisation observed in many graft patients with contact lens wear.

The central corneal sensitivity of the graft cornea was significantly reduced in 12 patients in agreement with previous studies.^{23,24} However, three of our patients (3, 5, and 12) had normal sensitivity post-operatively, with one patient having normal sensitivity only 13 months after penetrating keratoplasty. In another study Ruben and Colebrook²⁴ found no case of normal central sensation until at least three years after surgery.

The reduction in the graft eye sensitivity could partly be explained by an abnormal nerve regeneration pattern. Nerve fibres in the graft cornea are single axons running in the basal epithelial plexus, where they give rise to a profuse plexiform network with very few stromal nerves evident.^{23,25} Stromal nerves find it difficult to regenerate, as Schwann cell channels are not in apposition within the incision and incomplete sensory recovery in humans results

despite epithelial reinnervation.²³ There is also evidence of some neurological control of the corneal epithelium in both the resting state and when it is physiologically challenged.^{4,26,27} Our findings of depressed epithelial metabolic activity in association with incomplete recovery of corneal nerves following keratoplasty lend further support to the hypothesis that normal corneal epithelial metabolism partly depends on normal innervation.

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Corneal and intraocular penetration of topical and subconjunctival fusidic acid

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SUMMARY Corneal tissue absorption and intraocular penetration of fusidic acid were assessed in the rabbit after topical or subconjunctival application. Corneal tissue levels of fusidic acid one hour after the last topical application of the drug were well above the minimum inhibitory concentrations (MICs) for most Gram-positive and many Gram-negative organisms. Adequate levels were achieved in the aqueous at one hour following the last topical application, but no significant levels were detected in the vitreous. The corneal tissue and aqueous levels declined at 12 and 24 hours following the last drug application, however, corneal tissue levels at 24 hours were considered to be above the MICs for most Gram-positive organisms. A single subconjunctival injection of 100 mg of fusidic acid produced levels above the MICs of most organisms in the cornea, aqueous, and vitreous which persisted over 24 hours, but subconjunctival injection of fusidic acid at this concentration resulted in conjunctival necrosis and corneal decompensation. Fusidic acid penetrates well into avascular tissue and fully penetrates corneas with both intact and debrided epithelium, as evidenced by the intracameral drug levels. Good corneal penetration and absence of known topical toxicity make fusidic acid suitable for the treatment of microbial keratitis caused by susceptible organisms.

Fusidic acid (Fucidin) is an antibiotic isolated from the fermentation products of the fungus *Fusidium coccineum*. It is chemically related to cephalosporin P1 but has no cross-reactivity with any other commonly used antibiotics. Since its introduction in 1962 fusidic acid has been used systemically for the treatment of severe staphylococcal infections and topically for skin infections. It has the greatest antistaphylococcal (both beta-lactamase positive and negative) activity of any antimicrobial agent currently available.^{1,3}

The topical ophthalmic fusidic acid preparation (Fucithalmic) would be expected to be effective against Gram-positive organisms and many Gram-negative eye pathogens including *Neisseria* spp., *Moraxella* spp. *Haemophilus aegyptius*^{2,4,6} as well as *Mycobacterium*^{1,7} and *Chlamydia*.⁸ Fusidic acid is especially effective against staphylococci which are predominant in the aetiology of Gram-positive

bacterial keratitis. Fusidic acid can penetrate avascular tissue even in large collections of pus,^{9,10} making it an attractive antibiotic for the treatment of bacterial keratitis. The present study was designed to assess the corneal tissue, aqueous, and vitreous levels of fusidic acid following topical application or subconjunctival injection.

Materials and methods

ANIMALS AND METHODS OF TREATMENT

Forty-two New Zealand White male rabbits weighing 4 to 5 kg each were divided into three groups. Group A consisted of 18 rabbits in which a 5.5 mm diameter area of corneal epithelium was debrided in both eyes under topical anaesthesia. A Greishaber trephine was used to mark the area, and a No. 15 Bard Parker blade and Q tip swabs were used to remove the epithelium. All right eyes received a loading dose of fusidic acid 1% viscous eyedrops, one drop every minute for five minutes, followed by one drop every hour for the next 10 hours. The left eyes received

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placebo (the vehicle of the viscous eyedrops without fusidic acid) and had the same dosage schedule as the right eyes. Group B consisted of 18 rabbits which were treated in the same manner as those in group A, but the corneal epithelium was left intact. Six rabbits in each of the two groups (A and B) were killed by an overdose of pentobarbital at 1, 12, and 24 hours after receiving the last eyedrop. Group C consisted of six rabbits which received a subconjunctival injection in the right eye of 100 mg of fusidic acid in 0.5 ml of 0.9% sodium chloride at the beginning of the study. The left eye of each rabbit served as a control and was given a subconjunctival injection of 0.5 ml of 0.9% sodium chloride. Two rabbits were killed at 1, 12, and 24 hours after the subconjunctival injection of fusidic acid.

COLLECTION OF SPECIMENS

Immediately after the rabbits were killed peripheral blood was obtained by cardiac puncture. The blood was allowed to clot and was centrifuged at 3000 g for 10 minutes to obtain the serum. Before the intraocular fluid samples were obtained, the globe of each animal was rinsed with 0.9% sodium chloride to remove any remaining antibiotic. Aqueous was drawn with a 30 G needle attached to a tuberculin syringe inserted into the anterior chamber via a puncture at the limbus of each globe. Vitreous samples were obtained by inserting an 18 G needle attached to a 3 ml syringe into the midvitreal cavity 4 mm posterior to the limbus at the 7 o'clock position and withdrawing 1 ml of vitreous fluid. After anterior chamber and vitreous taps the corneas were excised at the limbus leaving no scleral rim. All specimens were frozen and stored at -80°C until the bioassays were performed.

DETERMINATION OF FUSIDIC ACID LEVELS

The levels of fusidic acid were determined in a masked fashion by an agar plate diffusion method with a reference preparation of diethanolamine fusidate as standard. Filter paper discs (Whatman AA, 6 mm diameter) were used for the standard dilutions and were compared with the serum, aqueous, and vitreous samples, which were placed on the surface of agar plates seeded with either *Sarcina lutea* ATCC 9341 or *Corynebacterium xerosis* FF as test organisms. Corneas were weighed and placed directly on to the seeded agar plates. Zones of inhibition were measured and the values were obtained by comparison with the standard dilution. The values obtained for the cornea samples were adjusted to levels per 100 mg of tissue. Fusidic acid is highly protein-bound (95-99%), and the results express the total amount, both free and protein-bound, of antibiotic. The sensitivity of the biological assay is 0.02 µg/ml of fusidic acid.

Table 1 Fusidic acid concentrations in topical fusidic acid treated and placebo treated eyes with intact corneal epithelium

	Fusidic acid	Placebo
<i>Cornea (µg/100 mg)</i>		
1 h Range	6.20-15.00	<0.02
Mean±SD	10.57±3.13	
12 h Range	2.20-8.40	<0.02
Mean±SD	4.65±2.31	
24 h Range	1.30-9.60	<0.02
Mean±SD	3.78±3.35	
<i>Aqueous (µg/ml)</i>		
1 h Range	0.21-8.20	<0.02
Mean±SD	3.22±2.84	
12 h Range	<0.02-0.28	<0.02
Mean±SD	0.17±0.24	
24 h Range	<0.02-1.50	<0.02
Mean±SD	0.25±0.61	
<i>Vitreous (µg/ml)</i>		
1 h Range	<0.02-1.30	<0.02
Mean±SD	0.25±0.52	
12 h Range	<0.02-0.66	<0.02
Mean±SD	0.10±0.27	
24 h Range	<0.02	<0.02
Mean±SD		

The Wilcoxon signed rank test was used to compare the mean values of fusidic acid in each sample group.

Results

Tables 1 and 2 present the results of the microbiobioassay of fusidic acid levels in the cornea, aqueous, and vitreous of the fusidic acid treated and placebo treated eyes with intact or removed epithelium at 1, 12, and 24 hours following the last application of eyedrop. The highest levels of fusidic acid were found in the corneas one hour after treatment. At this time debrided corneas had higher fusidic acid concentrations (63.81 (SD 85.69) µg/100 mg) than corneas with intact epithelium (10.57 (SD 3.13) µg/100 mg), but the difference was not statistically significant ($p=0.19$). After 12 hours the mean fusidic acid concentration in the corneal tissue was lower for both debrided (2.55 (SD 1.48) µg/100 mg) and animals with intact epithelium (4.65 (SD 2.31) µg/100 mg). The fusidic acid levels present at 12 hours were maintained through 24 hours in most animals (3.78 (SD 3.35) µg/100 mg with epithelium intact and 3.50 (SD 2.84) µg/100 mg with epithelium removed) ($p=0.88$). However, at 24 hours significant difference between treated and control eyes remained only in the epithelium intact group ($p=0.046$).

The aqueous humour level of fusidic acid at one hour showed no statistically significant difference ($p=0.660$) between the group with ablated epithelium (2.49 (SD 2.70) µg/ml) and that with intact epithelium

Table 2 *Fusidic acid concentrations in topical fusidic acid treated and placebo treated eyes with removal of corneal epithelium*

	<i>Fusidic acid</i>	<i>Placebo</i>
<i>Cornea (µg/100 mg)</i>		
1 h Range	4.50–232.00	<0.02
Mean±SD	63.81±85.69	
12 h Range	1.50–5.20	<0.02
Mean±SD	2.55±1.48	
24 h Range	1.20–9.00	<0.02
Mean±SD	3.50±2.84	
<i>Aqueous (µg/ml)</i>		
1 h Range	0.02–7.40	<0.02
Mean±SD	2.49±2.70	
12 h Range	<0.02–0.41	<0.02
Mean±SD	0.13±0.20	
24 h Range	<0.02	<0.02
Mean±SD		
<i>Vitreous (µg/ml)</i>		
1 h Range	<0.02–1.50	<0.02
Mean±SD	0.25±0.61	
12 h Range	<0.02–5.70	<0.02
Mean±SD	0.95±2.33	
24 h Range	<0.02	<0.02
Mean±SD		

(3.22 (SD 2.84) µg/ml). However, the aqueous level of fusidic acid was significantly higher than the aqueous humour levels of the placebo treated eyes ($p=0.05$ epithelium removed, $p=0.03$ epithelium intact). Minimal concentrations of fusidic acid could be detected in the aqueous of some animals at 12 and 24 hours after treatment, but these levels were not significantly higher than in the placebo-treated eyes.

The vitreous fusidic acid levels showed no statistically significant differences between the fusidic acid treated and placebo treated eyes at 1, 12, or 24 hours after treatment. Furthermore, there was no significant differences between the fusidic vitreous levels of the eyes with ablated and those with intact epithelium.

No detectable serum concentration of fusidic acid was present in any of the animals treated with topical fusidic acid.

Subconjunctival injection of 100 mg of fusidic acid in 0.9% sodium chloride produced high ocular tissue absorption in the cornea, aqueous, and vitreous (Table 3). The subconjunctival fusidic acid, however, caused severe conjunctival necrosis and corneal oedema, noted at 12 hours following the injection.

Discussion

Fusidic acid is considered to be one of the most effective antistaphylococcal agents available. It is effective against the β -lactamase-producing, methicillin-resistant, and multiresistant strains. Fusidic acid acts by inhibiting protein synthesis by

interference with the translocation step of peptide chain elongation and is bactericidal at concentrations close to the minimum inhibitory concentrations of 0.03 to 0.16 µg/ml.^{11,12}

Initially some concern arose regarding the rapidity with which some staphylococci develop resistance to fusidic acid in vitro.^{13,9} This finding, however, with rare exceptions, has not been reflected in the clinical eradication of infections^{9,10,15} and transfer of resistance from fusidic acid-resistant to fusidic acid-sensitive strains has not been detected.¹³ Nonetheless, combined therapy with antibiotics such as penicillin, methicillin, or erythromycin has been recommended by some investigators.¹⁴ It has also been noted that the presence of corticosteroids markedly reduces the antistaphylococcal activity of fusidic acid in vitro.¹⁵

Previous studies have shown that therapeutic levels of fusidic acid were present in the aqueous and vitreous of normal and inflamed eyes as early as 24 hours after oral administration of 1500 mg of sodium fusidate given in three daily divided doses.^{16,17} Intra-ocular penetration of fusidic acid occurs by simple diffusion across the blood-aqueous barrier and is not inhibited by carbonic anhydrase inhibitors. Owing to its ability to penetrate avascular tissue fusidic acid would also be expected to achieve high corneal concentrations when applied topically. In this study we found that topical application of 1% fusidic acid viscous eyedrops resulted in corneal tissue levels of fusidic acid well above the MICs for *Staphylococcus* spp., *Streptococcus* spp., *Corynebacterium*, *Haemo-*

Table 3 *Fusidic acid concentrations following subconjunctival administration of fusidic acid*

	<i>Fusidic acid</i>	<i>Placebo</i>
<i>Cornea (µg/100 mg)</i>		
1 h Range	871–1970	2.7–14
Mean±SD	1330±640	8.35±7.99
12 h Range	1.0–970	4.2–14.94
Mean±SD	486±674	7.49±10.53
24 h Range	439–946	2.6–8.7
Mean±SD	692±358	5.65±4.31
<i>Aqueous (µg/ml)</i>		
1 h Range	18–26	<0.02
Mean±SD	22±5.65	
12 h Range	15–23	<0.02–0.70
Mean±SD	19±5.66	0.35±0.49
24 h Range	12–19	<0.02–0.25
Mean±SD	15.5±4.95	0.125±0.18
<i>Vitreous (µg/ml)</i>		
1 h Range	3.9–5.2	<0.02–0.43
Mean±SD	4.55±0.92	0.21±0.30
12 h Range	9.4–15	<0.02–0.98
Mean±SD	12.2±3.96	0.49±0.69
24 h Range	2.7–21	<0.02
Mean±SD	11.8±12.9	

Table 4 Antibacterial spectrum of fusidic acid

Organism	Minimum inhibitory Concentration (µg/ml)
Gram-positive bacteria	
<i>Staphylococcus epidermidis</i>	0.13
<i>Staphylococcus aureus</i>	0.10
(penicillinase-producing)	
<i>Staphylococcus aureus</i>	0.05
(non-penicillinase-producing)	
<i>Streptococcus pneumoniae</i>	6.8
<i>Streptococcus pyogenes</i>	1.0
<i>Streptococcus viridans</i> group	1.6
<i>Streptococcus faecalis</i>	4.0
<i>Corynebacterium xerosis</i>	0.016
Gram-negative bacteria	
<i>Haemophilus influenzae</i>	3.2-25
<i>Haemophilus aegyptius</i>	0.20
<i>Neisseria gonorrhoeae</i>	0.40
(including β-lactamase-producing strains)	
<i>Neisseria meningitidis</i>	0.56
<i>Moraxella lacunata</i>	0.05
<i>Pseudomonas</i> sp.	>100.00
Miscellaneous	
<i>Chlamydia trachomatis</i>	4.0
<i>Mycobacterium tuberculosis</i>	1.0
<i>Nocardia asteroides</i>	2.5
Fungi	
<i>Candida</i>	>100.00
<i>Aspergillus</i>	>100.00
<i>Trichophyton</i>	>100.00

philus, *Neisseria*, *Moraxella*, *Chlamydia*, *Mycobacterium tuberculosis*, and *Nocardia* (Table 4).

The above concentrations were obtained in the corneas of New Zealand white rabbits one hour after a loading dose of one drop of the 1% fusidic acid given each minute for five minutes followed by one drop every hour for 10 hours. Corneal tissue penetration was higher, but was not significantly different in corneas in which the epithelium had been removed before administration of the antibiotic. Fusidic acid was found to penetrate the full thickness of the cornea as shown by the presence of significant levels of fusidic acid levels in the aqueous. The vitreous of some animals contained adequate levels of fusidic acid. This, however, was not a consistent finding, and no statistically significant difference could be found in comparison with placebo treated eyes. Serum samples failed to reveal the presence of fusidic acid in the systemic circulation following topical administration.

Although the fusidic acid had cleared the aqueous humour by 12 hours in most animals, significantly raised levels persisted for 12 hours in the corneas of the group with debrided epithelium and up to 24 hours in corneas with intact epithelium. These corneal levels were well above the mean inhibitory concentrations for *Staphylococcus* spp., most *Strepto-*

coccus spp., other Gram-positive organisms, and many Gram-negative organisms (Table 4).

A single subconjunctival injection of 100 mg produced high fusidic acid levels in the cornea, aqueous, and vitreous which persisted over 24 hours after treatment. However, severe conjunctival necrosis and corneal oedema resulted, thereby limiting the usefulness of subconjunctival administration of fusidic acid at this concentration.

The low toxicity of topical fusidic acid, along with the good corneal and intracameral penetration following topical administration established in this study, makes fusidic acid a promising therapeutic agent in the treatment of many types of bacterial keratitis, especially of staphylococcal aetiology.

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Visual function and pattern visual evoked response in optic neuritis

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SUMMARY The disparity between clinical visual function and pattern visual evoked response (VER) was studied in 53 patients who had suffered an attack of optic neuritis (ON) more than six months before. The visual functions tested included Snellen visual acuity, colour vision, visual field, and contrast sensitivity. The effect of pattern presentation, check size, and luminance was tested by recording VERs with several stimulus configurations. VER amplitudes were found to be associated with the outcome of all four clinical tests, independently of check size, luminance, or the presentation method used. On the other hand VER latencies were hardly ever related to the results of any of the four clinical visual tests. These findings support the idea that VER amplitude provides information about visual spatial perception, while VER latency is more related to the extent of demyelination.

Optic neuritis (ON) usually gives a characteristic clinical picture with a fairly favourable short-term prognosis in the majority of patients. Normal vision, as measured with a Snellen chart test, is regained in 50-80% of the patients within six months. In some cases, however, ON produces long-lasting visual dysfunction.^{1,2}

It has been suggested that Snellen chart tests are of questionable value for assessment of visual function in demyelinating disease, since they test only a restricted part of visual perception.^{3,4} The visibility of objects seems to be determined not only by how we see small details at high contrast, but also by how we discriminate between larger objects differing only slightly from their surroundings in colour and luminance. Hence some authors have suggested that the spatial contrast sensitivity function could be a more representative visual function in ON than the Snellen visual acuity.⁵⁻⁸

There is little doubt that the visual evoked response (VER) to a black and white pattern is a valuable means of tracing optic nerve lesions in patients suspected of multiple sclerosis (MS) or optic neuritis. A delayed latency of the first major positive

VER peak, found in 80-100% of clinically definite MS and ON patients, is a reliable indication of demyelination of the visual pathway.⁹⁻¹¹

Neima and Regan¹² tried to resolve some of the discrepancies between pattern VER and Snellen visual acuity by measuring the contrast sensitivity function. In general their results showed that abnormalities in the contrast sensitivity function could be used as a basis for predicting abnormalities in VER amplitude, while VER peak delay was less accurately predicted. The number of ON and MS patients they studied, however, was too small to permit meaningful statistical analysis. Neima and Regan¹² used two different stimuli for VER determination (with check sizes of 45 and 11 minutes of arc). It is now generally accepted that the pattern VER response depends not only on check size but also on luminance and method of presentation.^{13,14}

The object of the present study, like that of Neima and Regan,¹² was to search for correspondences between VER recordings and four clinical visual parameters: visual acuity, contrast sensitivity function, colour vision, and visual field. A previous study revealed a statistically significant relation between these parameters.¹⁵ In the present investigation pattern visual evoked responses were recorded by different methods of stimulation in order to see

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how check size, luminance, and method of presentation changed the possible relation between VER and the four clinical parameters.

Visual function in 53 patients with optic neuritis (ON) was tested six months to 4.5 years after the acute attack. This investigation was particularly interesting in those cases where Snellen visual acuity exceeds 1.0, suggesting (nearly) complete recovery of visual function. It was hoped that the large battery of tests used would permit more accurate estimation of just how much visual function had improved. The size of the group studied (106 eyes) permitted meaningful determination of the statistical correlations between the various test results.

Patients and methods

PATIENTS

Fifty-three ON patients, treated between 1980 and 1983 at the Eye Hospital Rotterdam, were re-examined in 1984–5 for this study. The patient group included 40 females and 13 males. Their age at the time of this study varied from 17 to 54 years (mean 32 years). The diagnosis of ON was based on the criteria summarised by Glaser.¹⁶

Eleven patients had a relapse of ON within the period 1980–4. In eight of them the recurrence affected the contralateral, initially unaffected eye, while in the other three cases the relapse was on the ipsilateral side. Thus a total of 61 eyes had had a clinical ON attack at the time of this study. All 106 eyes investigated were classified on the basis of clinical status and Snellen visual acuity to: unaffected, affected with recovery, and affected without recovery on the basis of the following criteria:

Classification	Clinical signs and symptoms in the eye during the ON attack	Snellen visual acuity during present study
Unaffected (n=45)	No	≥ 1.0
Recovered (n=33)	Yes	≥ 1.0
Non-recovered (n=28)	Yes	< 1.0

At the time of this investigation 29 of the 53 patients had clinical signs and symptoms of mild central nervous system involvement affecting structures other than the optic nerve, which was regarded as justifying the diagnosis of clinically probable or possible MS as defined by the criteria of McAlpine *et al.*¹⁷

METHODS

Visual evoked responses (VER) were obtained by checkerboard stimulation after correction of refractive errors.

Pattern reversal (PR) was achieved with a projector

system, the screen of which subtended a visual angle of 30°. Fast pattern reversal was obtained with the aid of an electromagnetically activated mirror.¹⁸ The squares of side 0.5° forming the pattern were presented with a mean luminance of 10 cd/m², those of side 1° with luminances of 10 cd/m² and 100 cd/m². Contrast between the checks was approximately 80% and the reversal frequency 1 Hz (i.e., 2 reversals per second).

Pattern (intermittent) presentation (PP) was accomplished with a TV monitor screen; the visual angle subtended was 16°. In this method the pattern was presented for 39 ms in each viewing cycle, with a repetition frequency of 2 Hz. The mean luminance of the screen both during and outside the pattern presentation was kept constant at 45 cd/m². The various patterns used had a check size (minutes of arc) and contrast respectively of 80'/80%, 40'/40%, 20'/20%, 10'/10%, and 10'/5%.

In both methods the patients were asked to look at a fixation spot at the centre of the stimulus field. In accordance with Halliday's method⁹ VERs were recorded with two occipital electrodes placed 2.5 cm and 5 cm above the inion (external occipital protuberance). A midfrontal electrode 12 cm above the nasion served as the reference electrode; the ground electrode was attached to the ear lobe. Two derivations were made, from each of the electrodes above the inion against the midfrontal one.

The bandwidth of the amplifiers was 0.166 to 70 Hz. In general 128 responses were averaged in all VER determinations. The output was fed simultaneously to an oscilloscope with a sweep time of 500 ms and to a minicomputer with a sampling time of 3.9 ms. With these techniques responses of 3 μ V or more could be discerned from the noise level. The VER thus obtained was recorded on an X-Y plotter.

Normal values were obtained from 47 healthy control subjects. For the latency the 90th percentile was taken as the upper limit of normal; for amplitude the 90th percentile was taken as the lower limit of normal.

The contrast sensitivity function was determined with equipment described previously.^{15,19} The automatic, microprocessor-controlled measuring procedure is based on a modified von Békésy tracking method,²⁰ which may be briefly described as follows. The stimulus (a vertical sinusoidal grating) is presented on a television monitor. The patient is asked to decrease or increase the contrast of the grating by pushing or releasing a button so as to hold it at his or her perception threshold. After eight reversals the average contrast is calculated and plotted, after which the spatial frequency is increased by a factor 2. The contrast sensitivity is determined over the range

from 0.1 to 25.6 cycles per degree (c/deg). The height of the stimulus is 5° and its width is 32° for the spatial frequency range from 0.1 to 0.4 c/deg (at a viewing distance of 50 cm) and 8° for spatial frequencies from 0.8 to 25.6 c/deg (200 cm viewing distance). To prevent after-images the grating is counterphased every 0.6 s. The mean luminance of the stimulus is 5 cd/m².

The stimulus is defined as: $C = (L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$, where $L_{\max}$ and $L_{\min}$ are the luminances of the light and dark 'bars' respectively. The contrast sensitivity is defined as the reciprocal of the contrast at threshold: $CS = 1/C(\text{thr})$.

The normal contrast sensitivity function was determined in 26 normal subjects (52 eyes) with the same age range as the 53 ON patients. The number of contrast determinations per eye was reduced to only three by averaging contrast sensitivities in the low (0.1–0.4 c/deg), medium (0.8–3.2 c/deg), and high (6.4–25.6 c/deg) spatial frequency ranges. A decrease of more than 2 standard deviations below the normal (average) contrast sensitivity for low,

medium, or high spatial frequencies is considered abnormal.

Visual acuity was determined with a Snellen chart and expressed as the reciprocal of the mean angle of resolution in minutes of arc. A visual acuity of 1.0 or more was considered normal.

Colour vision was examined under standardised conditions, with the Hardy Rand Rittler (HRR) and desaturated panel D-15 tests. Normal values were obtained from 25 control subjects, classified according to the classification of François and Verriest.²¹

Visual fields were determined with the computerised Octopus display. Visual field disorders were classified as central or paracentral absolute or relative defects.²²

Routine *clinical ophthalmological and neurological examination* was performed on all 53 patients.

Statistical analysis was performed with the SPSS computer program. Differences between sets of experimental data were tested for significance by the Wilcoxon, χ^2 , Kendall's b and t-c tests, and regression analysis.

Table 1 *Distribution of visual function abnormalities*

VER stimulus configuration		Low amplitude (μV)	High latency (ms)	Unaffected eyes (n=45)	Recovered eyes (n=33)	Non-recovered eyes (n=28)
<i>With PP presentation:</i>						
Check size (min of arc)	Contrast (%)					
80	80	<8.6	>192	1 9	2 12	17 14
40	40	<12.5	>195	5 12	8 17	21 19
20	20	<8.2	>222	11 12	16 11	22 20
10	10	<5.5	>198	12 16	14 18	23 25
<i>With PR presentation:</i>						
Check size (min of arc)	Luminance (cd/m ²)					
60	130	<7.9	>111	11 21	16 23	22 23
60	13	<6.9	>124	8 11	14 19	18 18
30	13	<6.3	>122	14 14	16 22	22 25
Total abnormalities in:						
VER				37	32	22
CS				12	13	26
Visual field				6	6	20
One or more visual functions tested:				No. 91	33 100	28 100

Row 1 tells us that, in the VER test using PP stimuli with, for example, check-size 80' of arc and contrast 80%, amplitudes less than 8.6 μV were taken as abnormally low. Such low amplitudes were found in one out of 45 'unaffected', two out of 33 'recovered', and 17 out of 28 'non-recovered' eyes. Row 2 tells us that in the same test latencies greater than 192 ms were high and found in 9, 12, and 14 eyes in the respective groups.

Results

VISUAL FUNCTION AFTER OPTIC NEURITIS

The results of clinical visual testing in this patient group have been described in greater detail elsewhere.¹⁵ A summary of these results, in combination with those obtained by pattern reversal (PR) and pattern (intermittent) presentation (PP) VER, is presented in Table 1.

A high percentage (96%) of non-recovered eyes showed at least one abnormal VER (either PP or PR). In only one eye did the VER results fall within the normal range. A similar high percentage of VER abnormalities (97%) was obtained in all affected eyes that had recovered ($n=33$). The most surprising result was that no fewer than 37 of the 45 unaffected eyes (82%) showed VER abnormalities (in latency, amplitude, or a combination of the two). A very small proportion of abnormal results may be ascribed to the 2% of normal subjects we may expect to find outside the normal range; this does not markedly affect the fact that the percentage of abnormalities found by PP (32%) and PR (56%) is strikingly high.

As was to be expected (and has been reported previously,¹⁵ all other visual tests gave the highest percentage of abnormal results in the non-recovered eyes and lower percentages in recovered and unaffected eyes.

The absolute number of VER abnormalities tends to be higher in those patients who had developed signs and symptoms outside the visual pathways, but the difference was not statistically significant (not shown in the tables). This tendency is in accordance with the previous findings for the four clinical visual tests.¹⁵

VISUAL EVOKED RESPONSE AND CONTRAST SENSITIVITY FUNCTION

In 47 eyes VER abnormalities (found by PP and/or PR) were observed in combination with an abnormal contrast sensitivity function. In six eyes both VER and contrast sensitivity were normal. This indicates that the results of VER and contrast sensitivity testing in all eyes investigated ($n=106$) overlap by no more than 50% (Table 2). The lack of a statistically significant association between overall VER and contrast sensitivity testing is disappointing (Table 2). We therefore examined these results in greater detail to see whether this could reveal some meaningful relationships between the two types of tests.

Consideration of VER amplitude and latency separately yields a more differentiated picture than that obtained by regarding overall results only. In Fig. 1 correlation coefficients are plotted for each VER stimulus and the contrast sensitivity function in the three frequency ranges considered. We use

Table 2 Relation between incidences of normal and abnormal VER and CS

Abnormal VER		Contrast-sensitivity-function		
With PP stimulus	With PR stimulus	Normal	Abnormal	Total
+	—	8	1	9
—	+	14	4	18
+	+	27	42	69
—	—	6	4	10
Total		55	51	106

A + in the first two columns refers to abnormal VER with the stimulus type indicated; a — in these columns refers to normal values. Thus row 3 tells us that 69 of the total 106 eyes showed VER abnormalities with both PP and PR stimuli. Of these 69 eyes 42 also showed CS abnormalities; the other 27 had normal CS (see text).

CS(L) to denote the contrast sensitivity function in the low frequency range, CS(M) for that in the medium frequency range, and CS(H) for that in the high frequency range. The results can be summarised as follows: there is a significant association (with alpha one-sided=0.05; $n=53$) between CS(L), CS(M), and CS(H) on the one hand and VER amplitude on the other, while VER latency is not significantly related to CS in any of these frequency ranges with the exception of the relation found between 10'-10% latency on the one hand and CS(L) and CS(M) on the other. The association between CS(L) and CS(M) and VER amplitude is stronger for middle sized checks (PP: 20'-20% and 40'-40%) than for the smaller (10'-10%) and larger (80'-80%) checks, while CS(H) and reduced VER amplitude is strongest for small check sizes (10'-10%).

VISUAL ACUITY, COLOUR VISION, AND VISUAL FIELD

An association between reduced visual acuity and abnormalities in visual field and colour vision on the one hand and contrast sensitivity abnormalities on the other has been previously reported.¹⁵ In the present study we were interested in the relation between VER results and those of the above mentioned clinical tests. Since colour vision and visual field are assessed as 'normal' or 'abnormal', we cannot express the association between these clinical test results and the VER results in terms of correlation coefficients. The quantity plotted in Fig. 2, middle and right columns, is therefore the 'phi' coefficient, which does provide a measure of such associations.

Inspection of Fig. 2 shows that reduced VER amplitude (in both PR and PP tests) is associated with abnormal results in all four clinical tests, whereas VER latency does not show any such association.

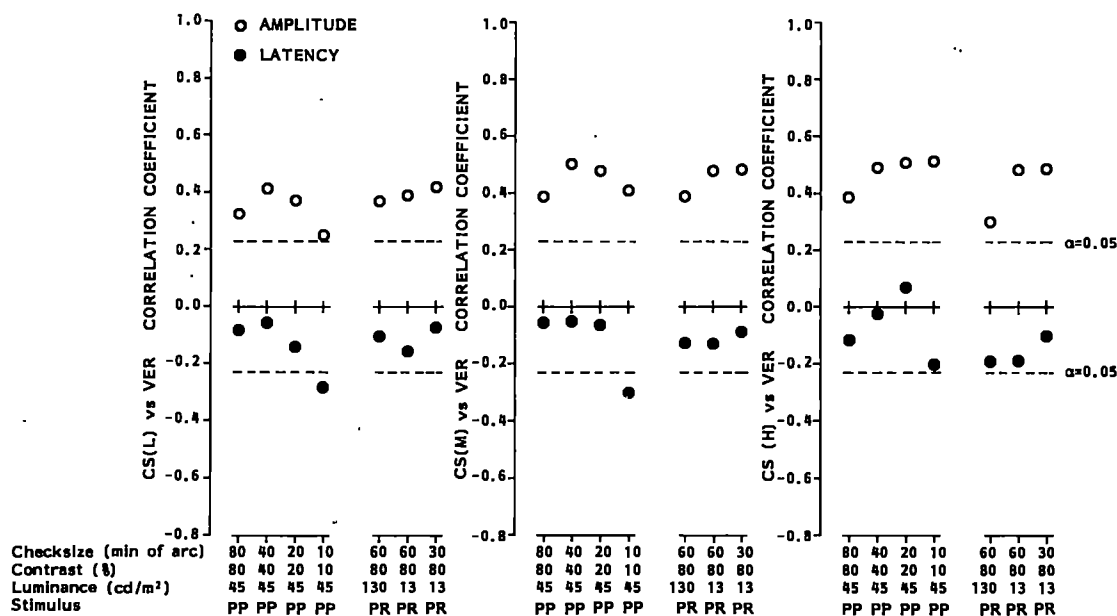


Fig. 1 Association between contrast sensitivity for several frequency ranges and visual evoked response (VER) for various stimulus configurations (details given under each graph). The frequency ranges are: Left: low (CS(L); 0.1–0.4 c/deg). Middle: medium (CS(M); 0.8–3.2 c/deg). Right: high (CS(H); 6.4–25.6 c/deg). The correlation coefficients between the broken lines are not significantly different from zero (χ^2 double-sided=0.10; $n=53$).

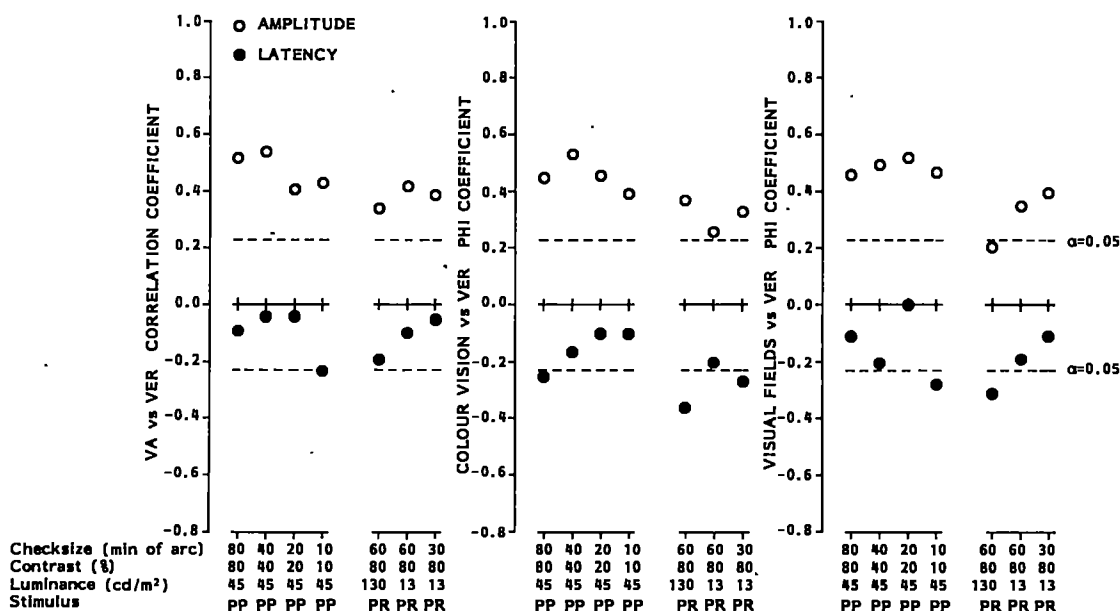


Fig. 2 Association between several clinical visual function tests and visual evoked response (VER) for various stimulus configurations (details given under each graph). The visual function tests are: Left: Snellen visual acuity (VA). Middle: colour vision (PD15 or HRR test). Right: visual fields (determined with the computerized Octopus display). The correlation coefficients (left) or the phi coefficients (middle and right) between the broken lines are not significantly different from zero.

Discussion

COMPARISON WITH PREVIOUS STUDIES

It is well known that, in optic neuritis (ON), visual evoked response (VER) is not closely related to sensory visual loss as determined with Snellen charts.^{23,24} It has been suggested that the 'hidden visual loss' which presumably exists in such cases may be detected by psychophysical tests which provide a measure of contrast sensitivity, visual field, and colour vision.^{15,25,26} Comparison of the results of these tests with VER measurements often revealed a considerable degree of overlap in ON or MS patients.²⁷⁻³¹ However, differences become apparent if VER latency and amplitude are considered separately.³² Neima and Regan¹² made this distinction in their attempt to correlate visual acuity, contrast sensitivity, and VER findings in ON and MS patients. They reported that reduced contrast sensitivity at high spatial frequencies was associated with reduced visual acuity and amplitude reductions in small-check VER tests. In all eyes where the contrast sensitivity was reduced at all spatial frequencies they found amplitude reductions in both small-check and large-check VERs, and diminished Snellen visual acuity. In the present study Snellen visual acuity and the other psychophysical test results were compared with VER latency and amplitude separately in all cases.

VISUAL EVOKED RESPONSE AND VISUAL TESTS IN ON

In general Figs. 1 and 2 indicate that VER amplitude is correlated with the results of all three psychophysical tests and with the Snellen visual acuity, while VER latency shows no such correlation.

In this study VER recordings were based on stimulation by checkerboard patterns with a variety of check sizes and luminance contrasts. Moreover, as we have seen, two different methods of checkerboard presentation were used (PR and PP). As mentioned in the introduction to the present paper, this wide variety of stimulus parameters was adopted in the hope that it would allow more precise detection of possible associations between clinical visual tests and VER. We found that VER results in response to pattern presentation of medium-sized checks with 40% luminance contrast gave the highest correlation (0.4–0.55) with contrast sensitivity for all spatial frequency ranges as well as with colour vision and with visual acuity.

Of particular interest was the finding that all but one of the 33 ON eyes classified as 'recovered' at the time of this study (visual acuity >1.0) showed a VER abnormality (either in amplitude, latency, or combination of the two). Seventeen of these 32 eyes also

gave abnormal results in one or more psychophysical tests. This indicates that VER recording is the most sensitive test for detecting hidden visual disturbance in ON (or MS). This conclusion is supported by the results of all tests of the 45 unaffected eyes. In our previous report¹⁵ we stated that 67% of these eyes gave abnormal results in one or more psychophysical tests. When we add the results of our VER investigations, we find over 91% of all *unaffected* eyes show abnormality in at least one test.

Our finding in the present study that reduced Snellen visual acuity and defects of colour vision and visual field are associated with diminished VER amplitude, but not with prolonged VER latency, is in line with our previous report that contrast sensitivity is associated with visual acuity, visual field, and colour vision.¹⁵ It is therefore not surprising that contrast sensitivity is related to VER amplitude and not to VER latency.

One of Neima and Regan's suggested explanations¹² for the discrepancy between Snellen visual acuity and VER in ON concerns the difference between the eye's ability to see fine detail (measured by what we call CS(H)) and coarse detail (measured by VER with large check stimulation). This would indicate that the association found between VER and contrast sensitivity would depend mainly on check luminance and/or check size. However, in the present study the associations between the results of clinical visual tests and VER recordings hardly depended on stimulus configuration at all.

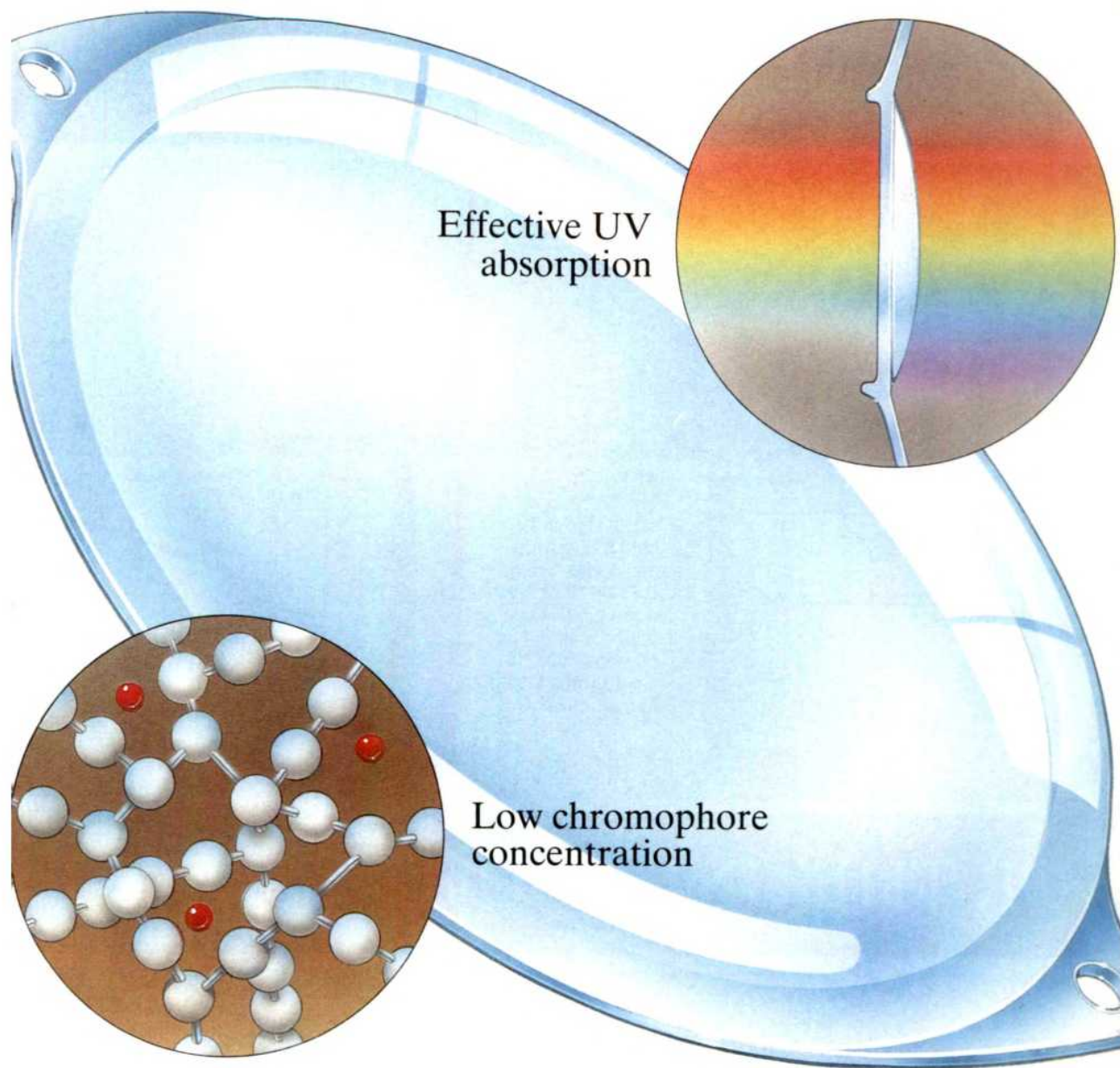
A more fundamental difference between the physiological mechanisms underlying visual acuity and VER latency must thus be at the root of the above-mentioned discrepancies. The VER latency is assumed to be related to the conduction velocity within the visual neural system. Chronic demyelination of the optic nerve will reduce the conduction velocity and hence prolong VER latency. However, there are indications that increases in VER latency can also be due to neurotransmitter deficiency.^{33,34} In contrast with this, VER amplitude is associated with all the clinical parameters (including Snellen visual acuity) used in this study and must therefore be related to the actual functional state of the retina and optic nerve fibres as regards spatial perception. This supports our assumption that VER latency and VER amplitude reflect different aspects of the visual system. The reason for the discrepancies between Snellen visual acuity (and other clinical visual parameters) and VER is thus perhaps to be sought in factors related to VER latency.

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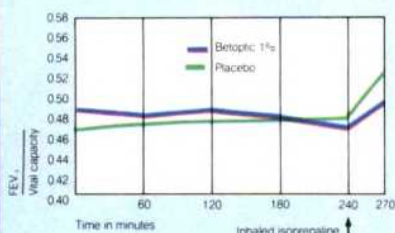
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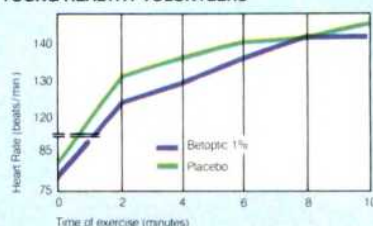
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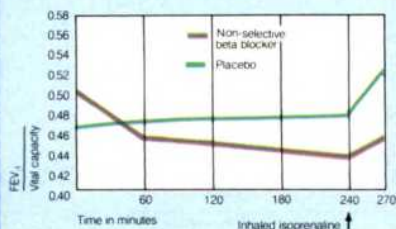


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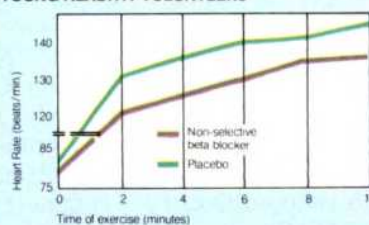
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Pasteurella multocida endophthalmitis

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SUMMARY We have recently seen an unusual case of endophthalmitis secondary to *Pasteurella multocida* infection. Unlike previously reported cases this patient had no previous history of animal bites or scratch wounds. Treatment included subconjunctival, parenteral, and intravitreal administration of ampicillin. Although the eye was sterilised, the patient's vision remained poor owing to the extensive amount of retinal necrosis.

Pasteurella multocida is a Gram-negative coccobacillus found in the upper respiratory tract of healthy domestic animals. The organism is transmitted to humans primarily via cat and dog bites or scratch wounds. We present the third reported case of *Pasteurella multocida* endophthalmitis and the first in which no animal contact had occurred.

Case report

A 61-year-old white male presented in February 1986 complaining of sudden loss of vision in his right eye. The patient's past medical history was significant for a seizure disorder, cirrhosis and chronic cellulitis of his left leg for the past four years. The patient denied a history of animal bites or trauma.

He had undergone phacoemulsification with implantation of an iris plane lens in the right eye in November 1977. Vitreous humour was lost at the time of surgery, so that he required an anterior vitrectomy. Postoperatively the patient developed mild cystoid macular oedema. However, his vision stabilised to 20/50. At the time of presentation his visual acuity was light perception in the right eye and 20/60 in the left eye.

Slit-lamp examination revealed a 2 mm hypopyon with heavy fibrin accumulation in the anterior segment and synechiae to the intraocular lens preventing pupillary dilatation (Fig. 1). Tensions by applanation were 34 mm Hg in the right eye and 14 mm Hg in the left eye. No red reflex was noted. B scan ultrasonography revealed dense vitreous debris, with the retina appearing flat. The clinical diagnosis was bacterial endophthalmitis.

Pars plana vitrectomy was performed three hours after presentation, but owing to poor visualisation of the posterior segment a total vitrectomy was not possible. Specimens collected at the time of surgery revealed no fungi, though many Gram-negative pleomorphic rods and polymorphonuclear leucocytes were present. Gentamicin 100 µg and cefazolin 2250 µg were injected intravitreally at the time of surgery. Cultures of the aspirated aqueous and vitreous humour were positive for *Pasteurella multocida*. The organism was isolated on blood and chocolate agar. There was no growth on EMB agar. Biochemical reactions were positive for glucose, sucrose, sorbitol,

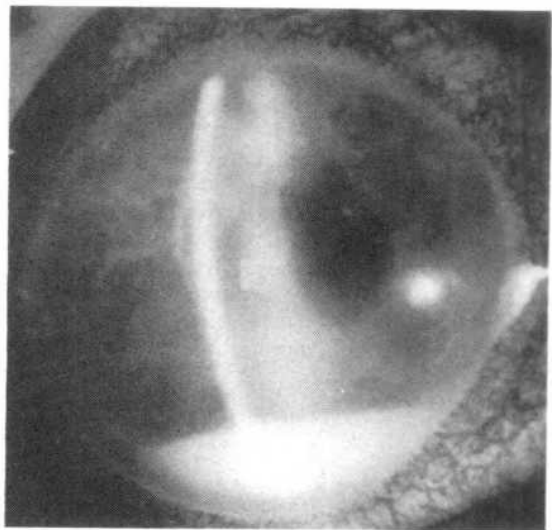


Fig. 1 20% anterior chamber hypopyon with fibrin covering the iris plane lens.

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urease, indole, nitrate, and oxidase. The patient was given 1000 µg of ampicillin intravitreally via a pars plana injection on the second postoperative day as well as intravenous ampicillin 3 g every six hours and prednisone 80 mg per day by mouth for 10 days. An additional 100 mg of ampicillin was injected subconjunctivally.

Topical therapy included prednisolone acetate 1% hourly and cyclopentolate four times a day. A second intravitreal injection of ampicillin 1000 µg was given on the third postoperative day, and two additional subconjunctival injections were administered on the third and fifth postoperative days. Three days postoperatively a vitreous tap was repeated and was found to be negative for organisms on culture and Gram stain. The anterior segment and anterior vitreous cleared three days after vitrectomy; however, only hand motions vision was achieved in this eye. Organisation of the posterior vitreous prevented visualisation of retinal detail. Cultures from the area of cellulitis of the patient's leg yielded a heavy growth of *Proteus mirabilis* and a light growth of *Staphylococcus epidermidis*, but there was no evidence of *Pasteurella multocida*.

Several weeks later repeat pars plana vitrectomy was performed to remove the vitreous opacification and explore the retina. At the time of surgery extensive vitreous strands and debris as well as severely necrotic retina were found. Repeat Gram stain and culture and sensitivity tests at this time were negative. The patient's visual acuity remained light perception six months postoperatively.

Discussion

To our knowledge only two other cases of *Pasteurella multocida* endophthalmitis have been reported. Serious *P. multocida* infections have previously been reported in association with wound infections from animal bites.^{1,2}

P. multocida endophthalmitis was reported by Galloway and Robinson² in an 11-year-old girl who sustained a scleral laceration from a cat scratch. This patient was treated with chloramphenicol and gentamicin drops as well as parenteral ampicillin and gentamicin. However, evisceration was necessitated because of continued bacteraemia and refractory endophthalmitis one month following the initial injury.

Weber *et al.*¹ reported the first case of *P. multocida* endophthalmitis in which excellent vision was preserved. The patient was a 10-year-old male who had multiple corneal lacerations due to a cat scratch. There were no signs of anterior or posterior segment infection at the time of surgical repair. However, *P. multocida* was grown from the vitreous and iris specimens. This patient responded to systemic ampicillin and cefazolin and never received the drug either intravitreally or subconjunctivally.

The decision to give our patient ampicillin was made because previous studies reported extreme sensitivity of this organism to the drug.³ The hypopyon and anterior vitritis cleared, suggesting that therapeutic levels of ampicillin were achieved in the aqueous through intravitreal, parenteral, and subconjunctival routes. Ampicillin has only rarely been used clinically in the vitreous cavity. Peyman experimentally has found that up to 10 mg of ampicillin given intravitreally is not toxic to the retina.⁴

So far there have been no reported cases of *Pasteurella multocida* endophthalmitis in a patient lacking a previous history of animal bites or trauma. This would suggest that the infection in this patient might have been endogenous. However, there was no evidence of another nidus for this infection and no leucocytosis was present. With aggressive antibiotic and surgical intervention, sterilisation of the eye was achieved. However, owing to the severity of the endophthalmitis at the time of presentation, the visual outcome was poor.

In summary, we present an unusual case of *Pasteurella* endophthalmitis in a patient with chronic cirrhosis and lower limb cellulitis. We advise intravitreal ampicillin early in the course of this infection to eradicate the organism.

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Aspergillus endophthalmitis

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SUMMARY A case is reported of bilateral aspergillus endophthalmitis in an infant without any detectable systemic predisposition or focus of infection. The patient is the youngest recorded case of endogenous aspergillus endophthalmitis so far, with an onset of symptoms at the age of 15 days. After histopathological confirmation of the aetiology by enucleation of the atrophic eye, systemic amphotericin B therapy was instituted with excellent results in the fellow eye. This is the first recorded instance of a complete clinical cure in aspergillus ocular disease on systemic amphotericin B therapy alone.

Aspergillus infections of ophthalmic interest usually cause keratitis or orbital cellulitis, and less commonly conjunctivitis and canaliculitis.¹ Aspergillus endophthalmitis, a relatively rare condition, has a devastating course, with blindness as its usual outcome. The clinical diagnosis is often difficult and the therapy is disappointing, with little or no reported success.²

This is a report of an infant with bilateral aspergillus endophthalmitis. As far as we are aware this is the youngest patient on record. The report is unusual in that the patient had bilateral ocular lesions in the absence of any detectable systemic predisposition or focus of infection elsewhere in the body. This is the first recorded instance of a complete clinical cure with good visual recovery in one eye brought about by intravenous amphotericin B therapy alone.

Case report

A 1-month-old male infant was brought to the hospital with complaints of redness, tearing, and a whitish reflex in the left eye of 15 days' duration. He had been born normally at full term, had no symptoms suggestive of bronchitis, pneumonia, or sinusitis, and had not received any systemic corticosteroid or antibiotic prior to his illness. There was also no history of any maternal disease.

On examination the left eye was grossly hypotonic, with evidence of atrophy of the bulb. There was marked ciliary congestion, and the cornea was hazy and the iris muddied. A greyish white mass extended through

the pupillary area into the shallow anterior chamber, obscuring the fundal glow. The anterior segment of the right eye was normal except for mild ciliary congestion, with a posterior synechia at 9 o'clock. The pupil reacted well to direct light. Fundus examination revealed haziness of the media with a non-rhegmatogenous retinal detachment involving the superotemporal, inferotemporal, and inferonasal quadrants. There were multiple superficial haemorrhages. A thorough systemic examination of the child revealed no focus of infection. Clinically a provisional diagnosis of bilateral endophthalmitis was made. However, the possibility of a bilateral retinoblastoma, with inflammation induced by tumour necrosis, could not be definitely excluded. The patient was started on systemic antibiotics and local corticosteroids, antibiotics, and atropine.

The total and differential leucocytic counts, sedimentation rate, and skiagram of chest, orbit, skull, and, optic foramina were found to be normal. The immune status was within the accepted limits of normal. There was a decrease in the number of T cells and T helper cells, with a marginal increase in B cells and T suppressor cells, a picture consistent with that of chronic inflammation (E-RFC, 23%; Sm Ig, 23%; OKT₃, 38%; OKT₄, 29%; OKT₈, 30%). Immunoglobulin electrophoresis was normal (C₄, 16 mg; IgA, Low; IgM, 208 IU; IgG, 97 IU). 'A' mode ultrasonography of the left eye showed a small eyeball with spikes of low to medium reflectivity throughout its extent, suggesting a gross disorganisation of the internal structures. 'A' scan ultrasonography of the right eye confirmed the exudative nature of the

Correspondence to Dr R Sihota.

retinal detachment without any evidence of a solid mass lesion.

The left eyeball was therefore enucleated. On sectioning the enucleated left eyeball the pus obtained from the vitreous cavity was cultured on Sabouraud's dextrose agar and glucose broth, but showed no bacterial or fungal growth.

The cytopathological examination of the aqueous from the right eye revealed polymorphs, lymphocytes, a few histiocytes, and some bare nuclei. There were no malignant cells. The lactic dehydrogenase activity was 14 units in the aqueous and 480 units in the serum.

Gross examination of the enucleated shrunken left eyeball revealed disorganisation of intraocular structures, with a large quantity of exudates in the anterior chamber and vitreous. On microscopic examination the anterior chamber was full of acute inflammatory cells and an eosinophilic exudate. The lens was fragmented, with the capsule being present in the pupillary area. The vitreous cavity was full of an acute inflammatory exudate consisting chiefly of neutrophils, occasional eosinophils, and necrotic debris. The retina and inner layers of the choroid were distorted and riddled with microabscesses showing a number of silver methanamine-positive septate hyphae, branching at acute angles. On the basis of these histological findings an aetiological diagnosis of aspergillus endophthalmitis was made.

The patient was given amphotericin B with heparin in the form of a slow intravenous drip daily to a total of 25 mg/kg body weight (140 mg), administered over a period of three months. Periodic monitoring of the blood cells, blood urea, serum creatinine, and electrolytes was done.

Regular examination of the right eye under general anaesthesia, showed a gradual improvement in the ocular condition. The superficial haemorrhages started disappearing in the third week of therapy and were totally absorbed by the end of the fifth week, though there was no change in the exudative detachment. During the eighth week the retinal detachment showed signs of resolution in the inferonasal area and had completely settled by the eleventh week. Three months after instituting the therapy peripapillary sheathing of vessels and a pigmentary stippling of the macula were the only abnormalities seen. The patient's vision appeared to be good. Periodic re-examination of the patient after every three months for a period of three years showed no signs of recurrence of the disease.

Discussion

Aspergillus endophthalmitis is rare and usually occurs in debilitated patients.^{3,4} Its clinical import-

ance stems from the fact that it has a very fulminant course, which may sometimes be markedly modified by specific therapy. However, the clinical diagnosis of the condition has been remarkably elusive, having been possible, preoperatively, in only one⁴ of the 23 cases reported so far. It is therefore important that the condition should be considered in the differential diagnosis of leucocoria, especially when some associated systemic features exist.

The patient described here is the youngest with *aspergillus endophthalmitis* to have been reported so far, having developed symptoms at the age of 15 days.⁶ A slight male preponderance exists in the number of reported cases, there being 13 males and 9 females. The case report by Lorenz⁷ gave no details.

The patient under discussion was unique in having a bilateral lesion, without any detectable predisposing factors. All the six bilateral cases reported so far had associated features such as prematurity and cytomegalic virus infection,⁶ rheumatic fever,⁸ aortic stenosis,⁹ Goodpasture's syndrome,⁴ or tuberculosis,¹⁰ suggesting the significance of underlying debility in bilateral spread of the disease. Four of these six cases also had systemic aspergillosis. It is difficult to speculate on the possible mode of infection in this infant. The fact that his left eye was more severely affected is in conformity with the observation that the left eye is more vulnerable to endogenous *aspergillus* disease (12 of the 16 unilateral cases). This is attributed to the direct origin of the left brachiocephalic artery from the aorta, providing direct access to intravascular pathogens. Another common predisposing factor, also absent in this infant, was the use of systemic antibiotics and steroids. Ten of the cases reported earlier were on antibiotics and steroids before the onset of ocular aspergillosis.

The clinical presentation in this case was not unusual. On review we found that the presenting complaint in the cases reported so far was a diminution of vision in 16 cases, a red eye in seven, ocular pain in four, and acute proptosis in two. Clinically, 12 cases presented with signs of iritis, five of whom had a hypopyon, and 18 showed marked chorioretinitis. A yellowish white mass with an abscess in the posterior segment was seen in 15 cases, while superficial retinal haemorrhages were present in three and a retinal detachment was observed in four. One case⁶ presented with an anterior chamber mass, quite akin to the picture presented in the left eye by this patient.

The definitive diagnosis of a fungal lesion rests on the demonstration of hyphae in the vitreous aspirate or in the histopathology specimen. Twenty of the reported cases had fungal hyphae in the vitreous cavity on histopathology, but only five were reported to give a positive culture. The aqueous tap from the right eye provided an initial clue to the inflammatory origin of

the pathology, while the classical histopathological features observed in the enucleated eye confirmed the diagnosis. The study of aqueous humour cytology and lactate dehydrogenase activity, in conjunction with a clinical picture of exudative detachment, retinal perivasculitis, superficial haemorrhages, and signs of iritis or endophthalmitis, should suggest the possible presence of this pathogen.

The almost complete reversal of the clinical picture in the right eye on medical treatment with intravenous amphotericin B was remarkable. No similar cure on antifungal therapy alone has been reported. This was attributed to the poor intraocular penetration of amphotericin B,¹¹ but our case has demonstrated otherwise, and this mode of therapy should be attempted more often. Various modes of therapy have been tried earlier, ranging from systemic iodides, intravenous and intravitreal amphotericin B, to a vitrectomy. The last two have given the best results, with resolution of the lesions in one case,⁵ but may themselves cause ocular morbidity.

The diagnosis of aspergillus endophthalmitis should be entertained in all patients with a systemic predisposition or aspergillus disease elsewhere in the body. The help of ancillary investigations such as ultrasonography, lactate dehydrogenase activity of aqueous and serum, aqueous humour cytology, and fungal culture should be utilised to establish a diagnosis. Medical therapy of fungal lesions with intra-

venous amphotericin B in these patients may prove helpful in salvaging reasonable sight in this otherwise almost hopeless condition.

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Post-traumatic and postoperative endophthalmitis: a comparison of visual outcomes

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SUMMARY We retrospectively studied 50 consecutive cases of exogenous endophthalmitis treated between 1972 and 1985. Twenty-two of these cases occurred after penetrating ocular trauma and the remaining 28 followed ocular surgery. Thirty-two (64%) of the cases were culture-positive. A wide variety of organisms were identified in the post-traumatic cases, while the isolated agent in the majority of postoperative cases was *Staphylococcus epidermidis*. Twenty-nine of the 50 patients received treatment with vitrectomy and intraocular antibiotics; of these, 14 (48%) achieved final visual acuities better than or equal to 20/400. Of the 21 patients who were treated with parenteral, topical, and subconjunctival antibiotics alone eight (38%) reached this same final visual acuity. Culture-negative cases, postoperative cases, and cases treated with vitrectomy and intraocular antibiotics were associated with improved visual outcomes.

Endophthalmitis complicating penetrating ocular injury generally has a worse visual prognosis than does postsurgical endophthalmitis.^{1,2} Several factors may account for the differences in final visual acuities between these groups, such as the virulence of the infecting organisms, the severity of any associated ocular trauma, and the rapidity of diagnosis and institution of appropriate therapy.¹

The use of intravitreal antibiotics and vitrectomy has improved success rates in the treatment of experimental and clinical endophthalmitis in selected cases.³⁻⁶ To understand better the factors affecting the prognosis of traumatic versus postoperative endophthalmitis we retrospectively reviewed 50 consecutive cases of exogenous endophthalmitis.

Subjects and methods

This study included 50 consecutive cases of exogenous endophthalmitis that had presented to the Department of Ophthalmology, University of Southern California School of Medicine, between July 1972 and July 1985. Criteria for clinical exogenous endophthalmitis included the following: a history of traumatic or surgical ocular penetration;

ocular pain; decreased visual acuity; conjunctival chemosis and hyperaemia; and anterior chamber or intravitreal inflammation.

Aspirates from either the aqueous or vitreous were obtained in each case. These samples were routinely placed on the following culture media: blood agar and chocolate agar (both incubated at 35°C in a 5% CO₂ atmosphere), thioglycolate broth (incubated at 35°C in air atmosphere), and Sabouraud's agar (incubated at room temperature in air atmosphere). If anaerobic bacterial cultures were requested, a brucella blood agar plate supplemented with vitamin K and haemin plus a laked blood agar plate with kanamycin and vancomycin were also inoculated and incubated anaerobically. A positive culture was interpreted as either growth of the identical organism on two or more media or confluent growth on one medium at the inoculation site.⁸ Identification of micro-organisms was carried out according to the *Manual of Clinical Microbiology*.⁹

All patients received extraocular (parenteral, fortified topical, and subconjunctival) antibiotics (EOABs). At our institution the addition of vitrectomy and intraocular antibiotics (IOABs) to the treatment regimens of selected cases began in 1977. Generally eyes with poor visual acuity (hand motions and worse) and advanced vitreous inflammation suggestive of infection were treated with

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vitrectomy and IOABs. In most instances, intravitreal administration of both a cephalosporin and an aminoglycoside was undertaken in these cases. B scan ultrasonography was routinely performed to assist in making the diagnosis of endophthalmitis and in planning for potential vitrectomy. Patients with painful, totally blind eyes underwent primary enucleation.

Results

Of the 50 cases 22 (44%) occurred after trauma and 28 (56%) occurred after ocular surgery. Twenty-eight (56%) of the patients were male and 22 (44%) were female. The mean age was 52 years with a range of one to 91 years. Thirty-two of the 50 cases (64%) had positive intraocular cultures.

Overall, 22 of the 50 patients (40%) achieved successful final visual acuities ('success' defined as a visual acuity of 20/400 or better). Of the 34 cases treated after 1977, 19 (56%) achieved successful visual acuities. Over the entire course of the study the visual outcome was successful in 14 of the 29 patients (48%) who were treated with vitrectomy and IOABs and in eight of the 21 patients (38%) treated with EOABs alone.

POST-TRAUMATIC GROUP (Table 1)

Of the 22 patients with post-traumatic endophthalmitis 15 (68%) were males and seven (32%) were females. The mean age was 29 years, with a range of one to 83 years. The severity of ocular trauma varied greatly: four patients sustained corneal lacerations with prolapse of intraocular contents; four patients had corneal or scleral lacerations with intraocular foreign bodies; and 14 patients had relatively uncomplicated corneal or scleral lacerations. The visual outcome was successful in six of the 14 cases (43%) treated with vitrectomy and IOABs

and in three of the eight cases (38%) treated with EOABs alone.

We were able to isolate and identify a wide variety of organisms from the intraocular aspirates in 13 of the 22 cases (59%) that had positive cultures. In four of these 13 cases (31%) multiple organisms were isolated; these included: *Klebsiella*, *Streptococcus*, *Escherichia coli*, *Clostridium*, *Neisseria*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. In the remaining nine cases the only single organisms were isolated; among these were *Staphylococcus epidermidis*, *Streptococcus*, *Candida*, *Propionibacterium acnes*, anaerobic diptheroids, *Staphylococcus aureus*, and *Bacillus cereus*.

Of the 13 cases that had positive intraocular cultures the visual outcome was successful in three of the nine (33%) that had been treated with vitrectomy and IOABs and in one of the four cases (25%) that had received EOABs alone. Of the nine cases that had negative intraocular cultures successful visual outcomes were noted in three of the five (60%) that had been treated with vitrectomy and IOABs and in two of the four cases (50%) that had received only EOABs.

Among the 12 eyes with final visual acuities worse than 20/400 five had initial trauma directly involving the posterior segment, two had an infection by a known virulent organism that responded poorly to treatment, and one had a retinal detachment after vitrectomy. In the remaining four cases there was no obvious factor predisposing to poor visual results; IOABs and vitrectomy had been utilised in the treatment of only one of these four cases.

POSTOPERATIVE GROUP (Table 1)

Of the 28 patients having postoperative endophthalmitis 13 (46%) were male and 15 (54%) were female. The mean age was 70 years with a range of 42 to 91 years. All of the primary operations involved the anterior segment only. These included: extracapsular cataract extraction plus intraocular lens (IOL) implantation, intracapsular cataract extraction plus IOL implantation, extracapsular cataract extraction alone, intracapsular cataract extraction alone, and glaucoma filtering procedures. The final visual acuity was successful in eight of the 15 patients (53%) treated with vitrectomy and IOABs and in five of the 13 patients (38%) treated with EOABs alone.

We were able to isolate and identify organisms from intraocular aspirates in 19 of the 28 cases (68%) of postoperative endophthalmitis. In three of these 19 cases (16%) multiple organisms were isolated; the remaining 16 (84%) had pure isolates of a single organism. *Staphylococcus epidermidis* was most frequently isolated (seven of 16 eyes). Other single isolates included: *Streptococcus pneumoniae*,

Table 1 Post-traumatic versus postoperative endophthalmitis

	Post-traumatic (n=22)	Postoperative (n=28)
Male: female	2:1	1:1
Mean age (years)	29	70
Mean onset to clinical evaluation (days)	3-4	1-6
Single aetiological agent: multiple aetiological agents	2:1	5:1
<i>Staphylococcus epidermidis</i> * aetiology	23% (3/13)	47% (9/19)
Final VA > 20/400		
Cases treated with VIT/IOAB	43% (6/14)	53% (8/15)
Cases treated without VIT/IOAB	38% (3/8)	38% (5/13)

*For culture-proved cases. VIT=vitrectomy, IOAB=intraocular antibiotics, VA=visual acuity.

Staphylococcus aureus, *Proteus*, and *Streptococcus*. Combinations of staphylococci and streptococci were isolated from all three of the eyes with mixed infections.

Of the 19 cases with positive intraocular cultures visual success was achieved in six of the 11 (55%) treated by vitrectomy and IOABs and in only three of the eight (38%) not receiving this treatment. Of the nine cases with negative intraocular cultures two of the four cases (50%) that were treated by vitrectomy and IOABs and two of the five cases (40%) receiving only EOABs achieved a final visual acuity of 20/400 or better.

Final visual acuities worse than 20/400 could be attributed to complications of surgical management (four eyes), patient refusal of therapeutic vitrectomy (two eyes), or infection by known virulent organisms that responded poorly to treatment (three eyes). The remaining six eyes that had a poor visual outcome did not have any obvious predisposing factors; IOABs and vitrectomy had been used in the treatment of only one of these six cases.

Discussion

Prior to the early 1970s infectious endophthalmitis often resulted in phthisis bulbi or evisceration.¹⁰ In 1974 Peyman and colleagues¹¹ demonstrated the safety and efficacy of IOABs in experimental endophthalmitis. Cottingham and Forster⁴ subsequently reported that treatment with IOABs in conjunction with pars plana vitrectomy was more beneficial than IOABs alone in cases of severe experimental endophthalmitis. Recently the use of both IOABs and vitrectomy in the management of infectious endophthalmitis has been shown to improve the visual outcome in most reported clinical series.⁴⁻⁷

In our series we reviewed 50 consecutive cases of exogenous endophthalmitis presenting between 1972 and 1985. The cases treated with vitrectomy and IOABs had better visual outcomes than did those treated with EOABs alone. This differential in visual outcome was observed in both culture-positive and culture-negative cases. Vitrectomy and IOAB administration thus appear to be rational therapeutic choices in selected cases with severe vitreal involvement, whether or not an aetiological agent is identified. Our overall success rate of 56% in cases of exogenous endophthalmitis treated after 1977 is similar to other recently reported series.¹²⁷

The reported success rates in treatment of post-traumatic endophthalmitis vary greatly, from 17% to 83%.²⁹ In our series we noted a success rate of 43% for 14 cases of post-traumatic endophthalmitis treated with vitrectomy and IOABs. Numerous prognostic factors may affect the visual outcome in

cases of post-traumatic endophthalmitis, including severity of the initial trauma, time interval between trauma and treatment, and virulence of the infecting organisms. These factors may account for the wide range of visual outcomes between reported series.

In contrast the success rates in cases of postoperative endophthalmitis vary little between recently reported series.²⁴⁷ Generally, these patients had all undergone primary anterior segment operations and were examined frequently in the postoperative period. Our success rate of 53% in cases of postoperative endophthalmitis treated with vitrectomy and IOABs compares favourably with these reports.

In our series the patients with postoperative endophthalmitis had better visual outcomes than did those with post-traumatic endophthalmitis (Table 1). In addition to the direct and delayed effects of the ocular trauma itself the worse visual prognosis in the post-traumatic group may be accounted for by the fact that these patients tended to wait longer before seeking treatment than did those with postoperative endophthalmitis. Furthermore, the post-traumatic infections were more likely to have been caused by multiple organisms. Rowsey and colleagues⁷ similarly observed that mixed infections occurred more frequently in post-traumatic than in postoperative cases of endophthalmitis; they also suggested that the combination of organisms may cause more visual loss than does any one species of organisms.

In summary, the results of this retrospective study support the use of vitrectomy and IOABs in cases of endophthalmitis with severe vitreal involvement. We found that the visual prognosis for eyes with post-traumatic endophthalmitis was worse than that for eyes with postoperative endophthalmitis. The increased virulence and multiplicity of organisms identified in the post-traumatic cases, as well as longer delays in seeking medical attention by patients in the post-traumatic group, are some of the factors that may explain these differences in visual prognoses.

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Intracameral gnathostomiasis: a cause of anterior uveitis and secondary glaucoma

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SUMMARY Recognition of parasitic diseases by Western physicians is becoming increasingly important because of increased international travel and the recent influx of refugees from South east Asia. We describe two patients who presented with acute anterior uveitis and secondary glaucoma caused by intracameral third stage larvae of *Gnathostoma spinigerum*. The parasites were successfully removed, with preservation of good visual acuity. The initial infection may occur through consumption of contaminated water and/or raw or undercooked foods, while the eyes may be involved even years later. Accurate diagnosis and surgical removal of the parasites may save life.

Human infestation by the spiruroid nematode, *Gnathostoma spinigerum*, has been frequently reported in Asia. The usual mode of infection is believed to be ingestion of raw, inadequately cooked or fermented fish or meat. Systemic manifestations include migratory cutaneous swelling and eosinophilic myeloencephalitis. Ocular involvement occurs incidentally to systemic migration of the parasite and may occur years after the initial infection. The increase in tourism to, and refugees from, South-east Asia make it likely that cases of gnathostomiasis will become more frequent in the western hemisphere. We report two cases of intracameral third stage larvae of *gnathostoma* resulting in acute anterior uveitis and secondary glaucoma. In both cases the parasites were successfully removed and good visual acuity restored. Detection of parasites on ophthalmic examination and surgical removal may prevent further systemic damage and even death.

Case reports

CASE 1

A 61 year-old woman presented with an eight-day history of pain and loss of vision in her left eye. Two weeks previously she had noted a painful cutaneous

swelling on her left hand. The swelling disappeared several days later without treatment.

On examination the right eye was normal. Visual acuity in the left eye was hand movements. Intra-ocular tension was 40 mmHg. The anterior chamber contained a fibrinous exudate. An inactive, curvilinear, living parasite about 5 mm long was seen at the temporal side of the pupillary border (Fig. 1). Multiple fenestrations caused by parasitic migration were present on the iris surface.

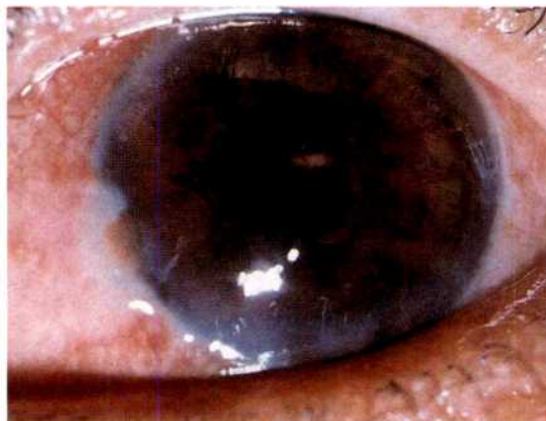


Fig. 1 Case 1. The living parasite about 5 mm long at the temporal side of the pupillary border.

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The patient was treated with oral glycerin and acetazolamide. The white cell count was $8.8 \times 10^9/l$, with 40% neutrophils, 51% lymphocytes, 3% monocytes, 5% eosinophils, and 1% basophils. Urine analysis and chest x-ray were normal.

Under general anaesthesia a corneoscleral section of 3 clock hours was made. The worm became active and migrated to the site of the surgical incision, where it was captured by its cephalic portion with lens capsule forceps. Postoperatively the patient was treated with topical dexamethasone, neomycin, and atropine, together with oral acetazolamide and prednisolone 30 mg daily. Her visual acuity improved to 6/18. Fundus examination revealed a normal optic nerve head and no evidence of parasitic tracks in the posterior segment. Over the following year a mature cataract developed in the affected eye.

The living parasite was transported in 0.85% NaCl to one of us (SP) for identification. It was fixed in 5% formalin and mounted in polyvinyl alcohol-lactophenol. It was identified as the third stage larva of *Gnathostoma spinigerum* and measured 4.5 mm long and 0.6 mm wide (Fig. 2).

CASE 2

A 32-year-old woman complained of blurred vision and pain in her left eye for one month. Two months previously she had had itching and cutaneous swelling around the left eye. Cellulitis presumptively caused by gnathostoma had been diagnosed and prednisolone 30 mg daily had been given for symptomatic relief.

Examination revealed visual acuity 6/60 in the right eye and 6/36 in the left. The intraocular tension was 17 mmHg in the right eye and 43 mmHg in the left. Old central corneal scars were present bilaterally. The conjunctiva of the left eye was injected and the cornea oedematous. The anterior chamber was clouded by a fibrinous exudate and an immobile, coiled worm approximately 5 mm long was present in



Fig. 3 Case 2. The inactive living parasite in the inferior portion of the anterior chamber.

the inferior portion of the anterior chamber (Fig. 3). Approximately 10 perforating holes caused by parasite migration were noted on the iris.

The patient was treated with oral glycerin and acetazolamide. The white cell count was $11.7 \times 10^9/l$, with 75% neutrophils, 14% lymphocytes, 4% monocytes, and 7% eosinophils. Urine analysis and chest x-ray were normal.

The parasite was removed from the anterior chamber as in the previous case and sent alive to one of us (SP) for identification. Postoperatively the patient was treated in the same manner as the first patient. Her vision improved to 6/24. The optic nerve head was normal and there was no evidence of a parasitic track. The lens has remained clear for two years.

The worm was processed as in the first case and identified as the third stage larva of *G. spinigerum*, 5.2 mm long and 0.7 mm wide. (Fig. 4)

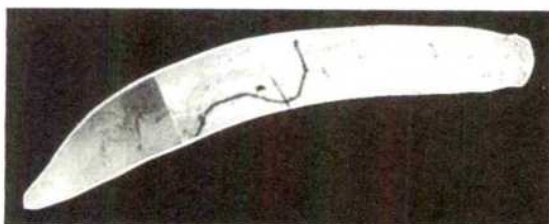


Fig. 2 Case 1. The worm consists of three parts. The stoma is anterior. The second part is the cephalic bulb, measuring 0.20 by 0.33 mm, and consisting of four rows of single pointed hooklets with rather smaller size in the first row of the anterior end. The third part is the body, consisting of many single pointed cuticular spines in transverse fashion with clearly seen cervical sac along oesophagus.



Fig. 4 Case 2. Composite microscopical picture of the third stage larva of *G. spinigerum*.

Discussion

Gnathostoma is an intestinal nematode of carnivores. *Gnathostoma spinigerum* is the most common tissue parasitic infection in Thailand and the second most common ocular parasite. The worm was first described in 1836 by Richard Owen, who discovered it in a stomach nodule of a tiger¹. The first human infection was reported in 1889 by Levisen (cited by Leiper²), who studied a single immature worm obtained from the breast abscess of a Thai woman. There have since been reports of immature worms recovered from skin, internal organs, nervous system, and eye.³ The first human case of intraocular gnathostomiasis was reported in Thailand by Rhithibaed and Daengsvang in 1957.⁴ Subsequently sporadic cases of intraocular infection have been reported from different parts of Asia.⁵⁻⁸

The central region of Thailand is one of the most important endemic areas of this parasite in Asia. Much of the food and drinking water in this region is obtained from fresh water rivers and lakes, and intestinal parasitic infestation is common.

The parasite lives encysted in the gastric mucosa of dogs, cats, and wild felines (Fig. 5). The red-orange worm measures about 4.5 mm long and 0.5 mm wide. The head bulb contains rows of hooklets and the body contains numerous spines. The ova are passed in faeces and hatch in fresh water to first-stage larvae. These are ingested by the copepod cyclops, the first intermediate host, in which the second-stage larvae develop. The cyclops are in turn eaten by fresh-water fish, frogs, snakes, and eels, the second intermediate hosts, in which the infective third-stage larvae

develop.⁹ Vertebrates such as cats and dogs complete the cycle. Man may become a facultative host by eating raw, infected intermediate hosts, such as fresh-water fish, frogs, and snakes. If intermediate hosts are eaten by paratenic hosts, such as ducks and chickens, the third stage larvae cannot undergo further development. They can, however, infect the paratenic hosts and in turn infect man if the paratenic hosts are eaten raw or insufficiently cooked. In Thailand more than 36 species of fresh water fish have been found to be infected with the third-stage larvae.¹⁰

The infection is more common in women than in men, perhaps owing to transmission via skin penetration during food preparation or from contaminated water containing infected copepods.¹¹ The third stage larvae cannot complete their cycle in man, and they migrate for years, causing inflammation in multiple organ systems.¹²

The clinical manifestations of gnathostomiasis include migratory cutaneous swellings, abdomino-pulmonary hypereosinophilic syndrome, and fatal eosinophilic myeloencephalitis.¹³⁻¹⁵ Damage may occur in any organ due to random migration of the parasite through the body. Recurrent migratory cutaneous swellings and eosinophilia in a patient living in or having travelled to an endemic area make the diagnosis likely. Symptoms often begin in the evening, perhaps due to increasing motility of the worms at this time. Skin testing with the third-stage larval antigen supports the clinical diagnosis when it is positive.

Despite the fact that the north-eastern region of Thailand is a major endemic area of gnathostoma reported cases of intraocular gnathostomiasis are rare. Lid swelling and intraocular parasites are the two major ocular manifestations, and may result in orbital cellulitis, uveitis, hyphaema, vitreous haemorrhage, and central retinal artery occlusion. The lid swelling is accompanied by itching, redness, and pain, which may be mild to severe. It is thought to be an allergic response occurring after the parasite has moved away, and it is useless to search for the parasite at that site. The intraocular parasite may be found in either the anterior or posterior segment. The larvae may migrate into the eye along the optic nerve or directly penetrate the sclera, resulting in traumatic retinal holes, vitreous haemorrhage, and iris perforation. Fibrous bands may extend from the point of entry into and through the vitreous. Most cases are presumptively diagnosed on the basis of the clinical picture, the high percentage of blood eosinophils, and the history of migratory swelling in relation to food habits and residence. Definitive diagnosis rests on the recovery and identification of the parasites.

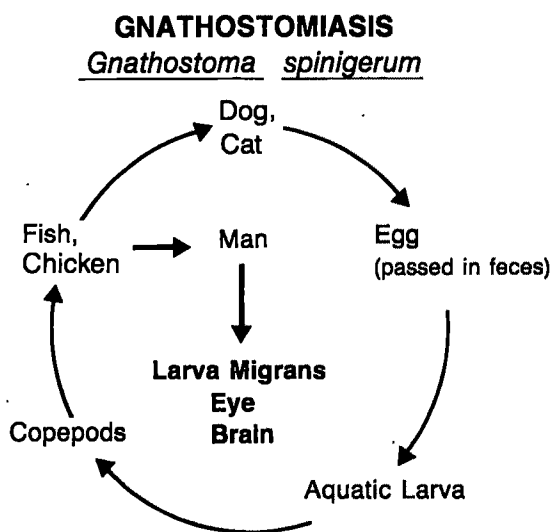


Fig. 5 Life cycle of *G. spinigerum*.

Our two patients had the same clinical pictures of acute anterior uveitis with secondary glaucoma but with normal eosinophils. The unusually low eosinophil count in our patients may be due to the fact that the parasites were in the anterior chamber, which is avascular, the cellular response therefore being much less than when the parasites are present in vascular tissues or spaces. The parasites were seen lying inactive in the anterior chamber. However, the numerous iris holes in both cases are suggestive of highly active worms at the initial stage of ocular involvement. In the absence of a visible parasite in the anterior chamber the presence of numerous iris holes can be the basis of diagnosis of parasitic ocular infestation. Anterior uveitis may be present after the parasite has migrated away. The fibrinous exudate and higher intraocular pressure may have led to the cessation of active migratory behaviour and thus to successful removal.

More commonly, removal of the parasite is thwarted by the escape of the parasite from the eye. Freezing the active worm with cryoapplication prior to its removal is usually considered in order to prevent death from systemic migration of the parasite. Failure to remove the parasite may lead to cerebrovascular accident if the parasite migrates into the central nervous system.¹⁶ To increase the success of removal, ocular manipulation should be kept at a minimum during the procedure. For this reason we favour removal under general anaesthesia instead of retrobulbar block. Corneal wetting and anterior chamber irrigation should be avoided as much as possible to minimise activation of the parasite.

There is no specific therapy other than surgical removal. Subcutaneous administration of Ancyrol (2,6-diodo, -4 nitrophenol) given subcutaneously has been effective in experimentally infected cats.¹⁷ Since the parasite can migrate rapidly, immediate surgery is required.

In our cases the parasites were successfully removed with lens capsule forceps without cryoprobe application. Intraocular tissue damage was slight in the first case, as hyphaema from an iris tear. Visual acuities were restored to 6/18 and 6/24 in the first and second patients respectively. However, complicated cataract with subluxation was later observed in the first patient and was attributed to the parasites rather than surgical trauma. The worms removed from the two patients were the third stage larvae.

The source of infective larvae in these cases could be from impure water or pickled fresh water fish.¹⁸ The abundance and variety of infected intermediate hosts reinforce the position of parasitic infections as a major health problem of Thailand.

Prevention depends on avoidance or adequate

cooking of such food as fresh water fish, snails, and pork. Better sewage disposal and the treatment of drinking water may prevent the spread of parasites in the community.

Gnathostomiasis is rarely diagnosed in Europe and the United States. However, not only may ocular involvement occur several years after the initial infection, but it may be the presenting sign of a previously silent infection.¹⁹ Increasing world travel, importation of food, and the influx of refugees from South-east Asia demand greater awareness of the parasitology of this region.²⁰ Gnathostomiasis should be included in the differential diagnosis of anterior uveitis with or without glaucoma in patients who have travelled to South-east Asia. Multiple iris perforations are diagnostic of a migrating parasite if none can be seen at the time.

G spinigerum may live for years in man, causing larva migrans and perhaps fatal eosinophilic myeloencephalitis. No antiparasitic drugs are available to treat ocular involvement, and therapeutic success depends on early and complete surgical removal. Because the eye is the only site at which direct visualisation and surgical removal are possible, ocular examination is crucial to proper diagnosis and treatment, which may be lifesaving.

This work was supported in part by the Glaucoma Foundation.

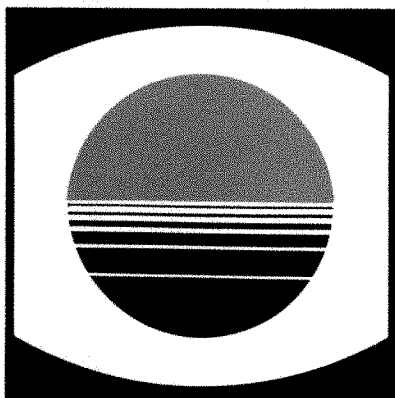
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The recommended dosage is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with Glauline 0.1%, changing to a higher strength if adequate control is not achieved or maintained. Patients on existing therapy, whether or not this is to be continued, should receive 0.3% Glauline and the intraocular pressure of all patients should be monitored regularly (e.g. every 4-6 weeks).

Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.

The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block.

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Histopathological characteristics of neodymium-YAG laser iridotomy in the human eye

MORTON F GOLDBERG, MARK O M TSO, AND MILAN MIROLOVICH

From the Department of Ophthalmology, Eye and Ear Infirmary, University of Illinois College of Medicine at Chicago, Chicago, Illinois, USA.

SUMMARY Light and electron microscopic studies of YAG laser iridotomies were performed in two human iridectomy specimens. Full-thickness defects were created and showed stromal and vascular necrosis. The light and electron microscopic configuration of the lesions was compatible with mechanical disruption from shockwaves. Thermal changes were absent in contrast to iridotomies created by argon laser photocoagulation.

Recent experience with Q-switched neodymium-YAG lasers suggests that photodisruption caused by plasma and shock-wave production is more effective than argon laser photocoagulation in creating permanent full-thickness iridotomies.¹⁻⁵ We therefore examined the light and electron microscopic appearance of such iridotomies in two human eyes in order to understand the short-term effects of Q-switched photodisruption in the iris.

Materials and methods

Twenty-four hours prior to elective cataract surgery and after we obtained informed consent, neodymium-YAG laser iridotomies were created in two patients with light-brown irides. The first patient was a 74-year-old white woman whose best corrected visual acuity was 3/400. She had 3+ nuclear sclerosis and 3+ posterior subcapsular cataractous changes. Using the Lasag Microruptor II and the Lasag contact lens (CGI) with methylcellulose, we created a full-thickness iridotomy without haemorrhage in the superior portion of the iris (Fig. 1). Laser settings were 4.9 millijoules, with two pulse trains of four

discharges aimed about 2 mm from the iris root. At the time of cataract extraction the involved sector of iris was removed for histological study.

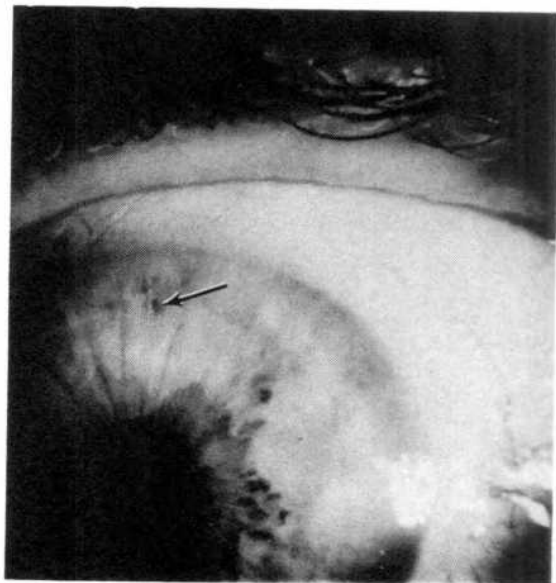


Fig. 1 Anterior segment photograph of the eye of patient 1 taken on the day of treatment. Neodymium-YAG laser iridotomy is marked by the arrow.

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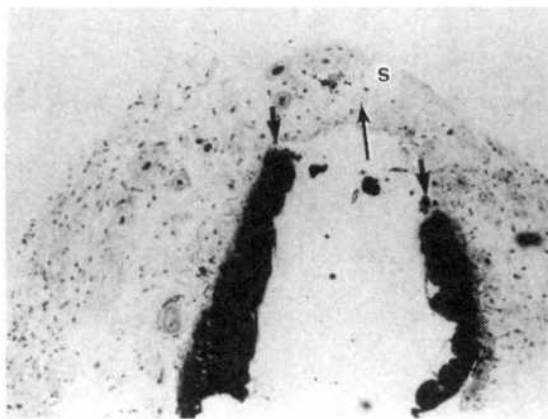


Fig. 2 Light micrograph of neodymium-YAG laser-induced iridotomy (patient 1) showing necrosis of the stroma (S) and blood vessels (black-and-white arrow). The dilator muscle and pigment epithelium are totally necrotic centrally (between black arrows). Damage is confined to the area immediately around the iridotomy. Mallory's stain.

The second patient was a 62-year-old white woman who had had diabetes for 40 years and was being treated with insulin. When initially seen three years before laser iridotomy she had prominent peripupillary rubeosis iridis and advanced epipapillary neovascularisation. The patient underwent panretinal photocoagulation at that time, and the rubeosis became much less prominent. Thereafter, progressive cataractous changes developed. Just prior to lens extraction the patient underwent Q-switched neodymium-YAG laser iridotomy with the Lasag Microruptor II. A contact lens (CGI) with methyl-cellulose was used. Two discharges of 6.0 millijoules

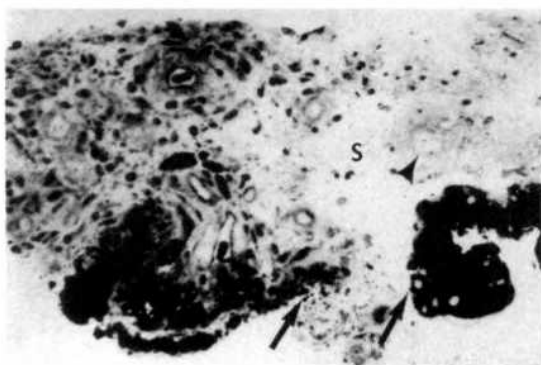


Fig. 3 Light micrograph of iridotomy created by neodymium-YAG laser (patient 2), showing necrosis of the stroma (S) and ghost outline of a necrotic blood vessel (arrowhead). The dilator muscle and pigment epithelium are necrotic (between arrows). Mallory's stain.

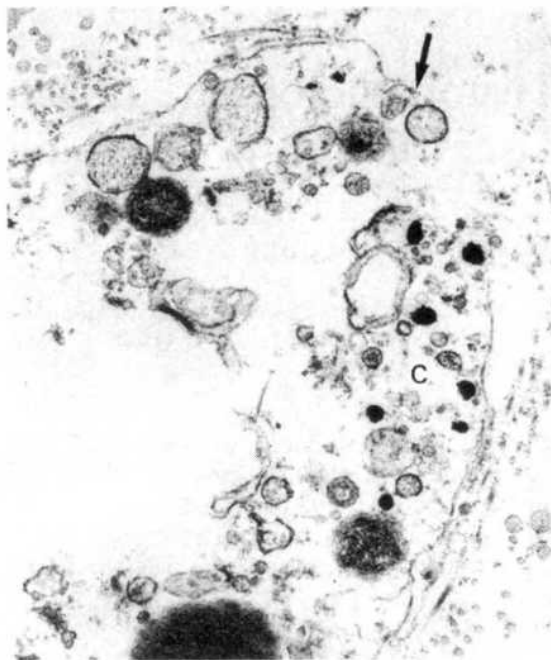


Fig. 4 Electron micrograph of a laser lesion (patient 1) illustrating lysis of a stromal cell with rupture of the plasma membrane (arrow) and watery cytoplasm (C).

with pulse trains of four discharges were directed at the iris, creating a full-thickness iridotomy. A tiny self-limited hyphaema occurred. The involved sector of iris was removed at the time of the cataract operation.

Results

Iris specimens from both patients were fixed by immersion in McDowell and Trumps fixative (1% glutaraldehyde and 4% paraformaldehyde), post-fixed in osmium tetroxide, dehydrated through graded alcohols, and embedded in Durcupan epoxy resin. Sections 1 μ m thick were prepared with Mallory's stain for light microscopy. Thin sections for transmission electron microscopy were stained with uranyl nitrate and lead citrate.

LIGHT MICROSCOPY

Both iris specimens (Figs. 2, 3) showed stromal necrosis in the areas of the full-thickness defects. Just peripheral to the necrotic regions were intact blood vessels. Within the areas of the laser induced defects the dilator muscles and pigment epithelia were absent. The tissue immediately surrounding the defects appeared totally necrotic, but more

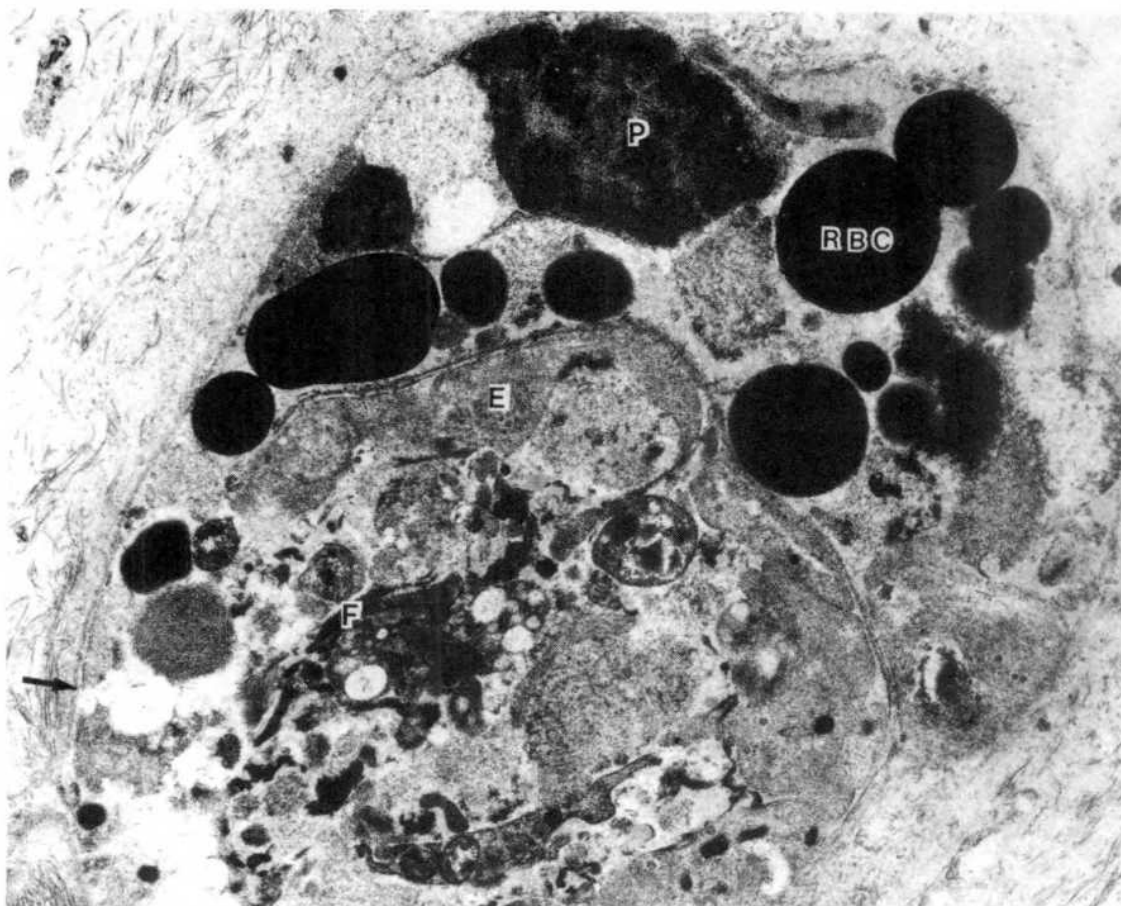


Fig. 5 Electron micrograph of iris of patient 1 showing disruption of a blood vessel with extravasation of red blood cells (RBC), fibrinous deposits (F) in an occluded lumen, and pericytic degeneration (P). The endothelial cells (E) are bordered by basement membrane.



Fig. 6 Electron micrograph of iris of patient 1 showing cuboidal configuration of vascular endothelium (E); S=stroma; P=pericyte.

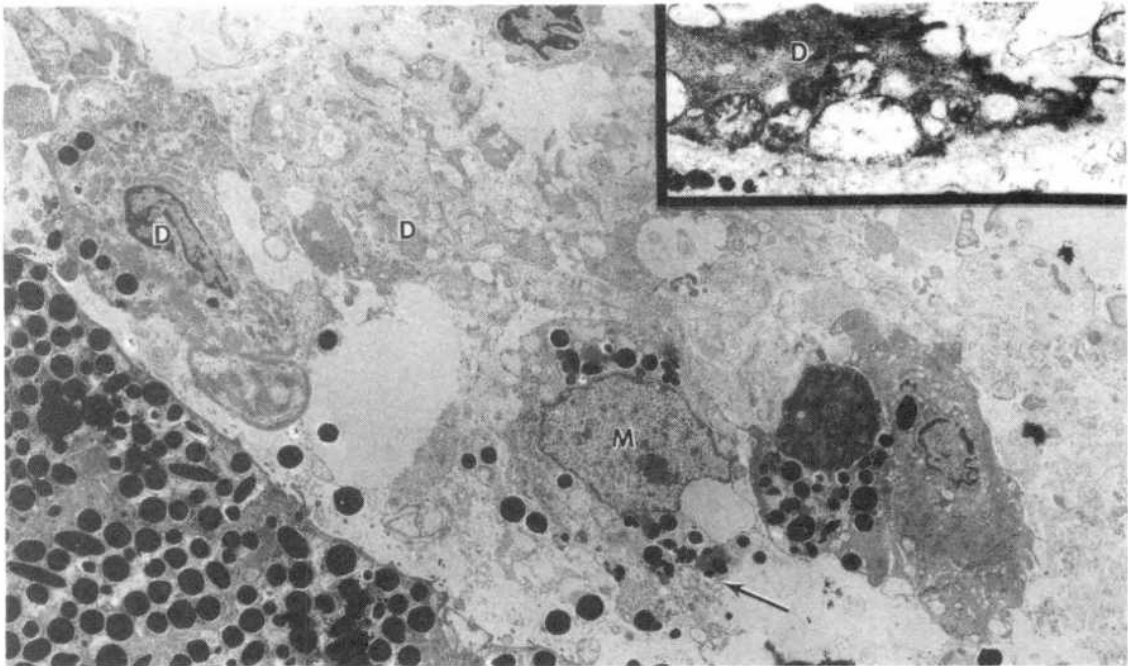


Fig. 7 Electron micrograph of iris of patient 1 showing dilator muscle (D) and pigment epithelial necrosis. A macrophage (M), which has phagocytised melanin granules, is present. The arrow points to phagosomes. Inset: Electron micrograph showing necrosis of the dilator muscle.

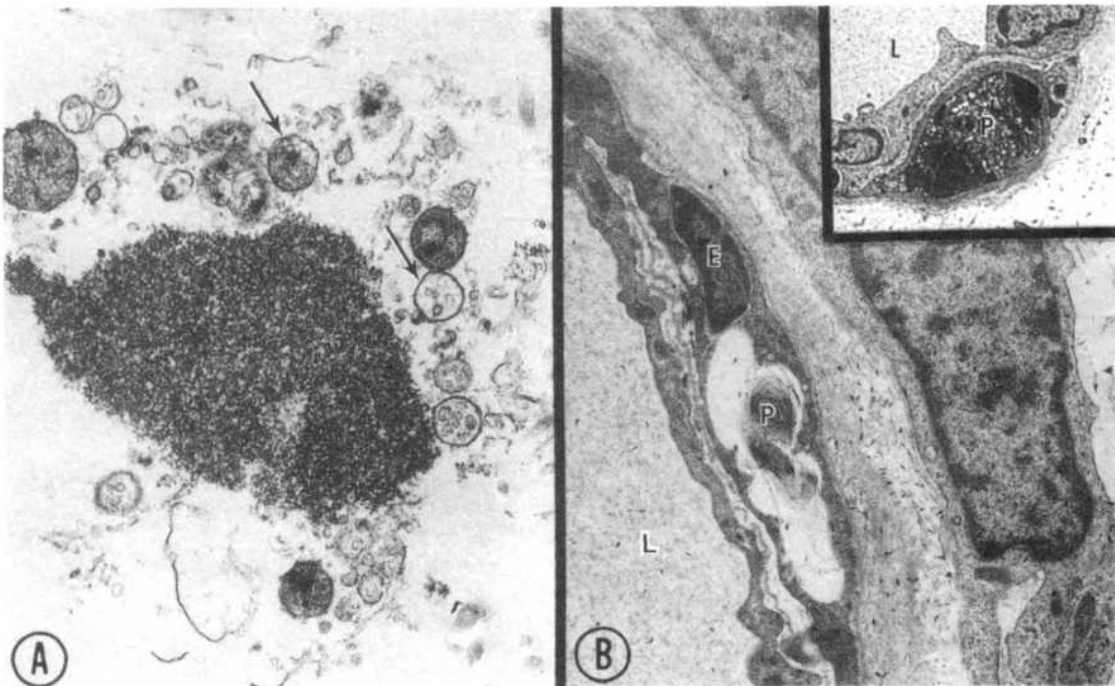


Fig. 8A: Electron micrograph of iris of patient 2 showing stromal cell lysis with rupture of plasma membrane and dispersion of cytoplasmic organelles (arrows). B: Electron micrograph illustrating pericytic degeneration. A lamellar body is seen in the pericyte (P). E=endothelial cell; L=lumen. Inset: Electron micrograph under higher magnification showing pericytic degeneration (P); L=lumen.

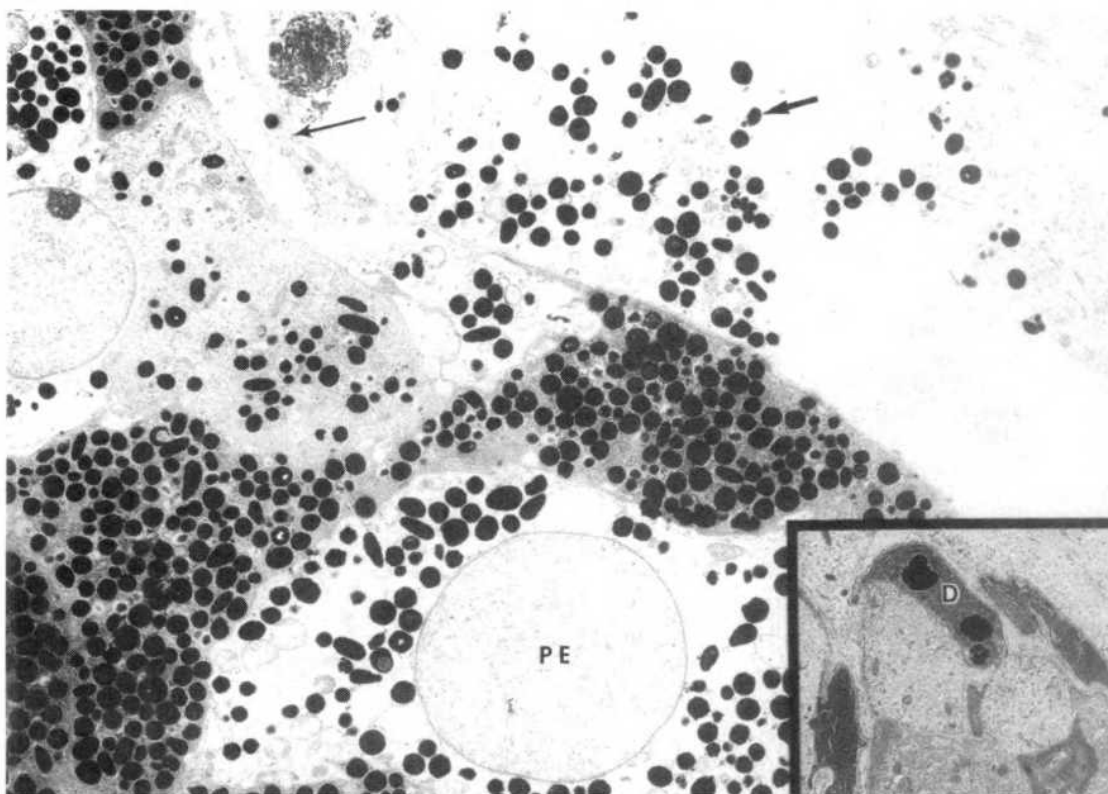


Fig. 9 Electron micrograph of iris of patient 2 showing pigment epithelial swelling (PE) and disruption with extrusion of melanin granules (black arrows) and rupture of plasma membrane (black-and-white arrows). Inset: Electron micrograph illustrating necrosis of the dilator muscle (D).

peripheral tissue looked normal. Free pigment granules were noted in extracellular locations.

ELECTRON MICROSCOPY

In the specimen from patient No. 1 there was lysis of stromal cells with rupture of the plasma membranes. The cytoplasm of these cells appeared watery (Fig. 4). Also noted were blood vessel disruption, extravasation of red blood cells, fibrinous deposits in occluded lumina, and pericytic degeneration (Fig. 5). Endothelial cells showed cuboidal configurations (Fig. 6). In addition the dilator muscle and pigment epithelium were necrotic. Macrophages were present and contained phagocytised melanin granules (Fig. 7).

In the iris specimen from patient No. 2 stromal cells also showed lysis, with ruptured plasma membranes and dispersed cytoplasmic organelles (Fig. 8A). Pericytic degeneration was noted, and one pericyte contained a lamellar body (Fig. 8B). The pigment epithelium was swollen and showed rupture of plasma membranes and extrusion of melanin

granules (Fig. 9). Dilator muscle necrosis was also observed in this specimen (Fig. 9, inset).

Discussion

Our findings confirmed theoretical considerations and prior observations in animals and humans regarding the shock-wave effects caused by the Q-switched neodymium-YAG laser.¹⁻⁸ The histopathological alteration was compatible with mechanical disruption. Thermal, coagulative changes were absent, in contrast to iridotomies created by argon laser photocoagulation. Surprisingly little reaction surrounded the lesions (although a few macrophages were present), possibly due in part to the short-term nature of the observations.

The iris pigment epithelium appeared more severely disrupted than the stroma. It is possible that the loosely organised stroma is more resilient and able to withstand the shock-wave effects of the Q-switched explosion better than the taut pigment epithelium.

Vascular lesions consistent with mechanical rupture were also present. The lack of a thermal, coagulative effect is characteristic of Q-switched explosions and is associated, both clinically and microscopically, by extravasation of red blood cells. Such bleeding rarely has clinical significance.

Our data are compatible with those of prior investigators² and confirm the value of the neodymium-YAG laser in creating full-thickness iridotomies. Damage to surrounding tissue is confined to the immediate area of the full-thickness defect. The lack of more peripheral damage may be important in minimising subsequent reparative efforts. Clinical experience suggests that iridotomies created with Q-switched explosions remain more open more often than do those characterised by the thermal denaturing effects of argon laser photo-coagulation. Iridotomies created by argon lasers usually require many more laser discharges than do those produced by neodymium-YAG lasers, and are associated with considerable inflammatory response.^{4,5} Fibroplasia is more likely to occur after argon laser iridotomy, and the rate at which iris openings become occluded is substantial. Neodymium-YAG lasers thus appear to be clinically more useful than argon lasers, because of their higher rate of persistently open iridotomies.

There are some risks to surrounding anterior segment structures when Q-switched explosions take place in the iris.⁹⁻¹¹ Evidence indicates that micro-punctures of the anterior lens capsule may occur, though this rarely seems to cause progressive opacification of the entire human lens.¹¹ In addition, if the iridotomy is created very close to the iris root, minor contiguous sites of damage occur in the corneal endothelium and trabecular meshwork.¹⁰ It is doubtful whether these events have clinically important

sequelae, but long-term quantitative observations have not been made.

Supported in part by Core Grant 1792 and Training Grant 7038 from the National Eye Institute, Bethesda, Maryland, and an unrestricted research grant from Research to Prevent Blindness, Inc., New York City.

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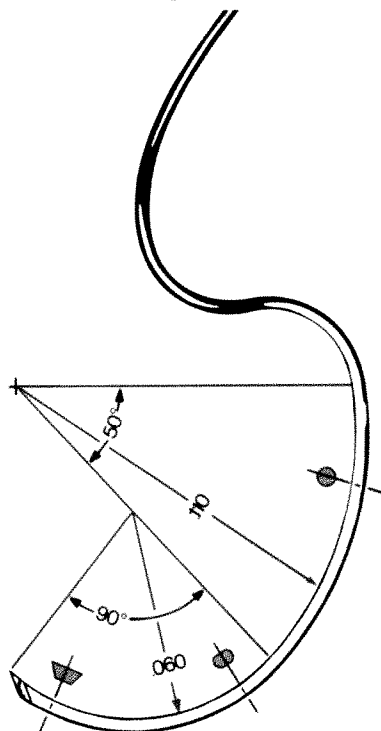
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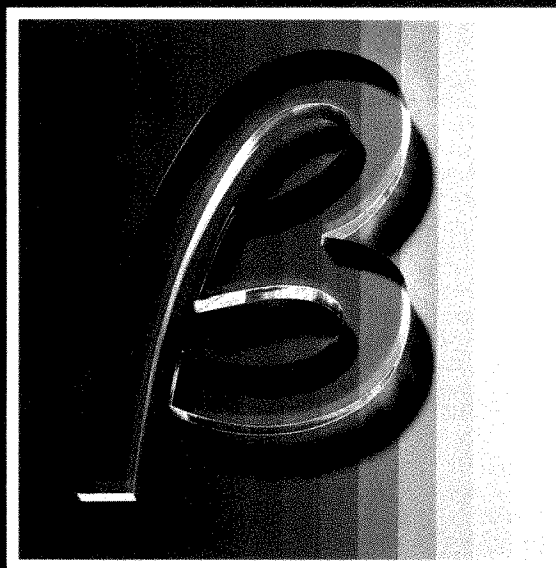
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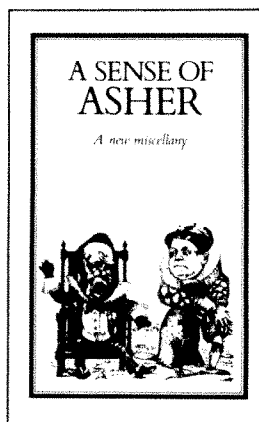
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Incontinentia pigmenti (Bloch-Sulzberger syndrome): seven case reports from one family

A. SPALLONE

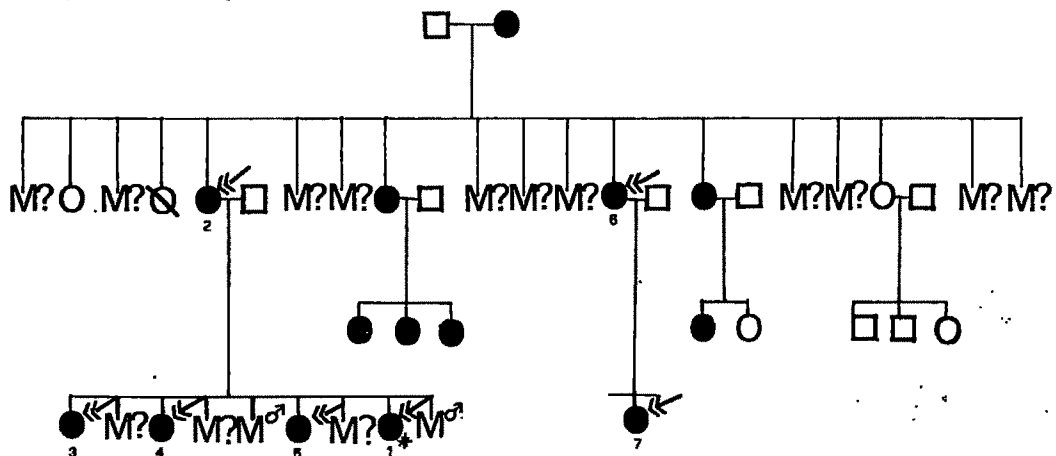
From the St Gerardo Hospital, Department of Ophthalmology, Monza (Milan), Italy

SUMMARY Seven members from a large family who showed signs of incontinentia pigmenti were examined. A clear X-linked dominant transmission was demonstrated, lethal in males. Study of this family shows that vascular abnormalities of the retina and disorders of the retinal pigment epithelium are the most important ocular lesions in the Bloch-Sulzberger syndrome.

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a genetic disease of the skin with generalised ectodermal and mesodermal dysplasia which may often involve the eyes (35% of the patients),¹ hair, teeth, and central nervous system. Skin lesions are

Correspondence to Dr A Spallone.

usually present at birth or shortly after in the form of erythematous eruptions with linear vesiculations. The final stage is characterised by irregular macular streaks of brown to slate-grey pigmentation, distributed asymmetrically on the torso and sometimes on the limbs.



●: Affected female

O: Not affected female

□: Not affected male

⊗: Dead for unknown cause

↔: Case reports

#: Proband

M?: Miscarriages of unknown sex

M♂: Miscarriages autoptically male

Fig. 1 Pedigree of family described.

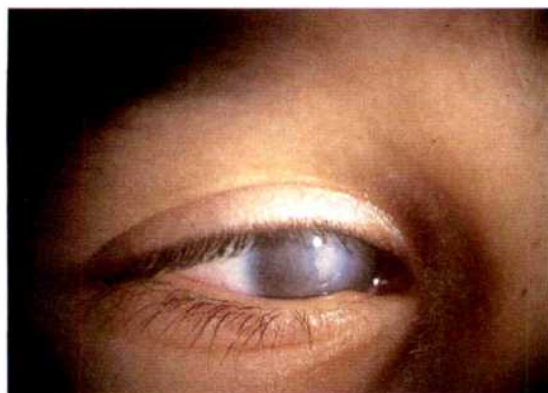


Fig. 2 Case 1. Right eye.



Fig. 3 Case 1. Left eye.

We have had the opportunity to study seven patients all of whom are members of one large family in which a total of 14 members were affected by incontinentia pigmenti. A clear X-linked dominant transmission was demonstrated, lethal in males (Fig. 1). The following seven case reports illustrate the most important ocular lesions of the disease.

Case reports

CASE 1

This was the proband. A female child, 4 years old, birth weight 3 kg. The parents were not related. The dermatological symptoms of incontinentia pigmenti appeared immediately after birth.

Ocular examination showed nystagmus, oedematous cornea, and cataract (Fig. 2) in the right eye, microphthalmus with iridolenticular synechiae and complete cataract in the left eye. In this eye the iris was atrophic, with pigment irregularities (Fig. 3).



Fig. 4 Case 1. Classic whorls and streaks of pigment on torso and in right eye.

Visual acuity was no perception of light in both eyes. Ultrasonography revealed the presence of bilateral retinal detachment with dense membranes in the vitreous. A general medical examination showed the classic whorls and streaks of pigment on the torso and on the right leg (Fig. 4). The grandmother had had 18 pregnancies, 11 of which had been miscarriages. The seven fullterm pregnancies were all resulted in females. Five of these had ocular and dermatological problems; one died of an unknown cause, and the last one was healthy. The first of these five affected patients is the mother of our proband.

CASE 2

Mother of the proband, 37 years old, who has been affected by incontinentia pigmenti since birth.

Ocular examination showed intermittent exotropia. The visual acuity was 1-0 in both eyes. Both lenses were clear. In the ocular fundus in the right eye no anomalies could be found; by contrast in the left eye the retinal vessels were anomalous. Towards the temporal equator both venules and arterioles became tortuous, slightly kinked, of an irregular calibre, increased in number, and with preretinal fibrosis. Apart from this area the peripheral temporal part of the retina was completely avascular (Fig. 5). In the inferior nasal area there were small alterations of the retinal pigment epithelium. On general medical examination we noted some pigmentary alterations of the skin, the absence of the lateral upper incisors, and a conical appearance of the other teeth. The patient had had nine pregnancies; five of these had ended in miscarriages, two of which during necropsy were found to be males.

CASE 3

Sister of the proband, 14 years old. Immediately after birth the patient developed the dermatological signs of incontinentia pigmenti.

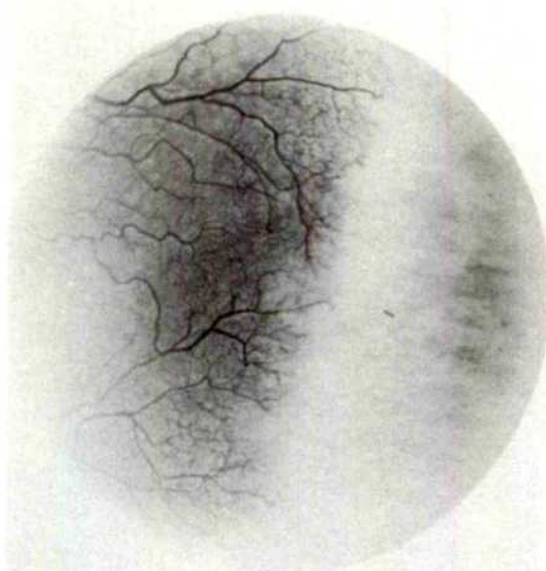


Fig. 5 Case 2. Fluorescein angiogram of left eye. In the temporal equator the retinal vessels are tortuous, slightly kinked, and increased in number. The peripheral temporal part of the retina is completely avascular.

Ophthalmological examination showed nystagmus and marked exotropia in the left eye. Visual acuity was 0.7 in the right eye and counting fingers in the left eye. The cornea and lens were both clear. The fundus in the right eye was normal. At the temporal equator



Fig. 6 Case 3. Fluorescein angiogram of the left eye, showing abnormal vascularisation of temporal peripheral retina.

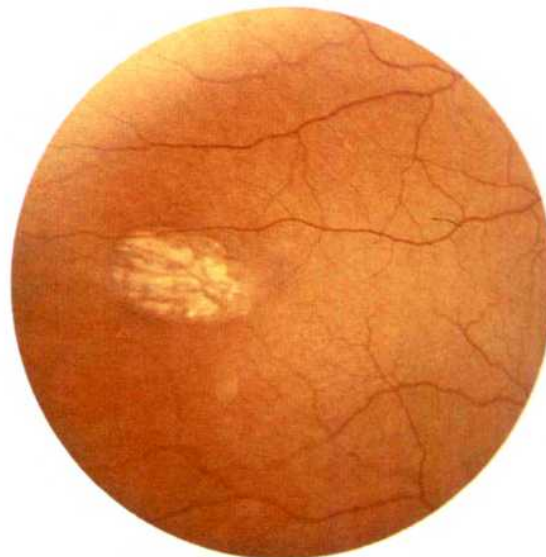


Fig. 7 Case 6. Fundus of right eye: alteration of pigment epithelium and choriocapillaris with sharp edges.

of the left eye the vessels arborised and connected in the form of an arteriovenous anastomosis, with preretinal fibrosis (Fig. 6). From this equatorial zone of abnormal vascularisation to the ora serrata the peripheral temporal part of the retina was avascular. In the sector inferior to the optic disc a small defect of the pigment epithelium was present.

This patient suffered from epilepsy and had spastic paralysis. In addition one half of the body was noted to be shorter than the other.

CASE 4

Sister of the proband, 10 years old. Incontinentia pigmenti from birth.

At the age of 3 months leucokoria was diagnosed in the right eye. This eye was enucleated because of suspected retinoblastoma. Visual acuity in the left eye as 0.8 with -3 sph. The ocular fundus in the left eye showed vascular abnormalities in the equatorial retina very similar to that of case 2. The peripheral temporal part of the retina was avascular. The typical pigmentary alterations of the skin were observed; dentition was incomplete, and some teeth were conical.

CASE 5

Sister of the proband, 8 years old, incontinentia pigmenti from birth. The anterior segment of the eyes was normal. Visual acuity was 0.6 in the right eye and 0.5 in the left eye. It was not possible to observe the ocular fundus in this patient.

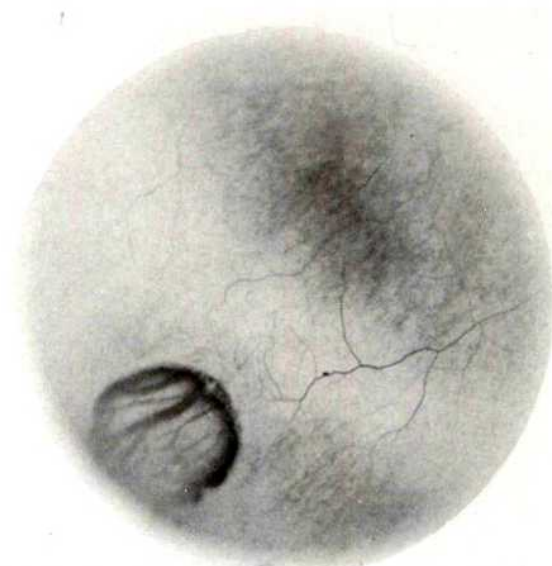


Fig. 8 Case 6. Fluorescein angiogram of right eye: in the temporal periphery a circular alteration of the pigment epithelium and choriocapillaris is present.

CASE 6

Aunt of the proband, 34 years old. Vesicular lesions and hyperpigmentation of the skin occurred two days after birth.

The right eye was exotropic. The visual acuity was 0.2 in the right eye with -3.75 sph and 0.8 in the left eye with -8 sph. The corneas and lenses were both



Fig. 9 Case 6. Fundus of left eye showing enormous atrophy of the pigment epithelium in the temporal quadrant.

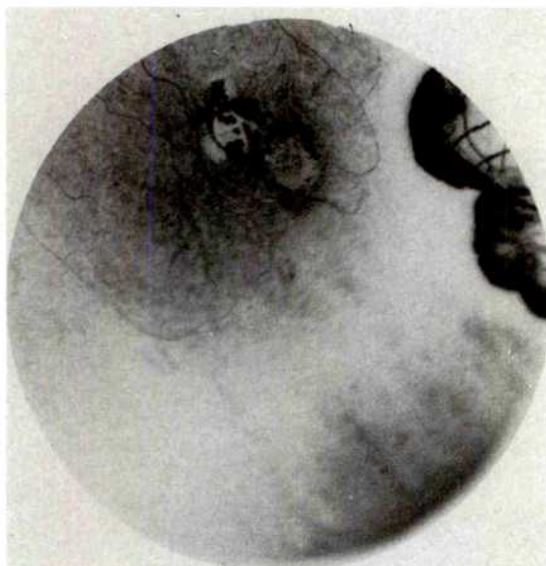


Fig. 10 Case 6. Fluorescein angiogram of left eye. Below the large atrophic area of the pigment epithelium are small alterations of the retinal vascularisation.

clear. Temporally to the macula a clearly defined change in the pigment epithelium and choriocapillaris with sharp edges was present (Fig. 7). In the temporal periphery another circular alteration of the pigment epithelium and choriocapillaris was visible (Fig. 8). This zone also showed mild anomalies of the retinal vascularisation. In the left eye it was possible to see a large region of atrophy of the pigment epithelium with sharp edges; it involved the whole temporal quadrant (Fig. 9). Just below this large area another small alteration of the retinal vascularisation was seen (Fig. 10). Apart from these changes, two other small atrophic patches were present. Toxoplasmosis was excluded by blood examinations. She had alopecia and abnormal teeth. The lateral incisors were missing (Fig. 11).

CASE 7

Daughter of case 6, 11 years old. Incontinentia pigmenti from birth.

Tilting of the head and strabismus in the right eye were noted at the age of 3 months. Cataract with retinal detachment were also diagnosed in this eye. Ophthalmological examination showed a blind microphthalmic right eye with cataract (Fig. 12). Ultrasonography revealed the presence of retinal detachment with dense membranes in the vitreous. Visual acuity was 1.0 with -1.50 sph in the left eye. In this eye the cornea and lens were both clear. The ocular fundus showed only a small patch of pigment epithelium atrophy without alteration of the



Fig. 11 Case 6. Abnormal configuration of the teeth.

retinal circulation (Fig. 13). She had marked dental anomalies, alopecia, and the typical streaks of pigment on the torso.

Discussion

The term *incontinentia pigmenti* was first used by Bloch¹ in 1926, when during a histological examination he observed abnormalities of the pigment cells of the epithelium of the skin, which were thought to be 'incontinent' of melanin. In 1938 Sulzberger³ found other ectodermal defects in association with this condition. In 1954 Franceschetti and Jadassohn⁴ divided the disorder into two types: the classic *incontinentia pigmenti* or Bloch-Sulzberger variety,



Fig. 12 Case 7. Microphthalmic right eye with complicated cataract.

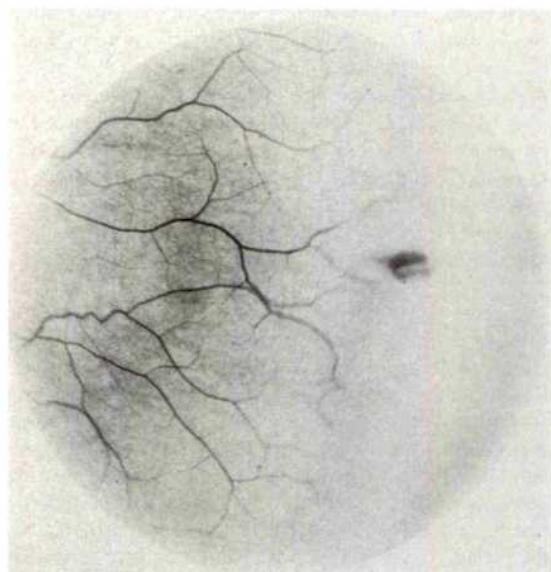


Fig. 13 Case 7. Fluorescein angiogram of left eye: small patch of pigment epithelium atrophy in the peripheral retina is present.

which occurs almost exclusively in females, and the Naegli type (or reticular) with a dominant mode of transmission, which involves both sexes without ocular malformations.

Our family clearly belongs to the Bloch-Sulzberger variety, and it is certainly the largest family ever described. Ocular abnormalities are generally found in 35% of the cases, and they probably represent the most severe systemic anomalies associated with *incontinentia pigmenti*. Our patients confirm this last point, and they illustrate the whole range of ocular lesions. One patient (case 4) underwent enucleation at 6 months of age because of suspected retinoblastoma. Our proband was completely blind. Myopia was present in three patients, strabismus with amblyopia in five, and cataract in three. It is interesting to note that cataracts were present only in the cases with retinal detachment, and they were probably caused by the retinal detachment. Microphthalmus was present in three cases, nystagmus in two. Ophthalmoscopically it was possible to see retinal abnormalities in four patients. In two other cases a dense cataract did not permit us to observe the fundus, but ultrasonography showed abnormalities of the vitreous, retinal detachment, and thickening of the choroid.

In three of our cases, characteristic and well marked changes in the retinal pigment epithelium and choriocapillaris were visible during ophthalmoscopy as of large plaques, which are probably analogous to those observed on the skin. No history

of trauma, retinal detachment, or toxoplasmosis was obtained.⁵ In two patients these changes were bilateral, and in case 6 they were visible, covering all the temporal quadrant in the left eye. Previously only four papers have reported alterations of the retinal pigment epithelium in incontinentia pigmenti.^{6,9} However, those alterations were limited, did not cover a wide area, and were less serious than ours.

In addition to pigment epithelium the retinal vascularisation can be seriously affected. We observed retinal vessels were sharply interrupted in the temporal quadrant, with an arteriovenous shunt; they were tortuous and irregular in calibre, without signs of occlusion. From this zone to the ora serrata the retina was completely avascular. One can assume that the temporal retina had failed to develop, producing areas of capillary non-perfusion with pre-retinal fibrosis. Contraction of this preretinal fibrotic tissue results in retinal detachment and multiple convoluted infoldings of the retina resembling retinal dysplasia, retinopathy of prematurity, posterior hyperplastic primary vitreous, and other disorders.

The retinal vascular abnormalities and the disorders of pigment epithelium are the most important ocular lesions in incontinentia pigmenti. Some authors^{8,10} have inferred a relation between retinal pigment epithelium anomalies and fibrovascular changes. However, our findings showed that this relationship is not so clear. In fact in case 6 there was a noticeable alteration of the retinal pigment epithelium and few vascular defects. By contrast in cases 2 and 3 we noted serious defects of the retinal

vessels and few alterations in the retinal pigment epithelium. The anomalies of the retinal vessels and retinal pigment epithelium may perhaps represent independent alterations in the development of the retinal vascularisation and the retinal pigment epithelium, and not necessarily be related.

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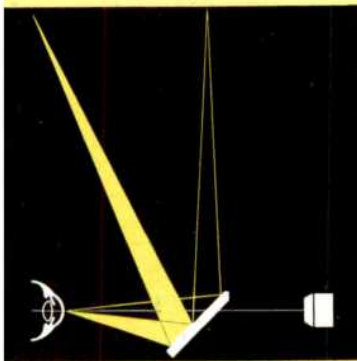
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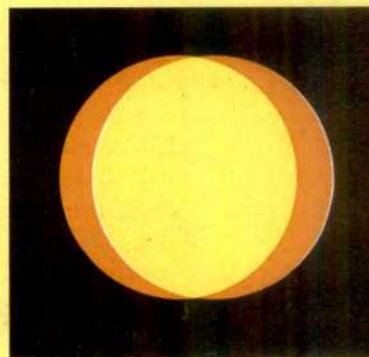
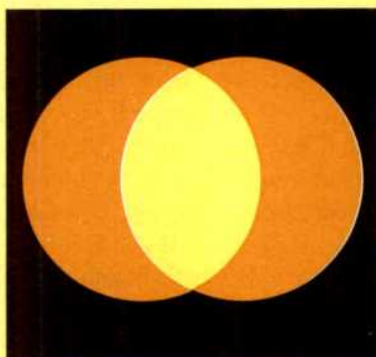
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Clinical anophthalmos

M O'KEEFE, M WEBB, R C PASHBY, AND R D WAGMAN

From the Department of Ophthalmology, the Hospital for Sick Children, Toronto, Canada

SUMMARY We report on 15 patients (10 boys, 5 girls) with clinical anophthalmos. Two of them had bilateral anophthalmos, 10 had systemic anomalies, and six had abnormalities of their remaining eye. Only two appeared to have an associated underlying aetiology. Fourteen patients underwent orbital reconstruction or socket enlargement with varying degrees of success. Our own experience suggests that unnecessary lid procedures should be avoided, but we recommend early prosthetic fittings. We feel that a multidisciplinary approach is necessary to attain useful rehabilitation.

Anophthalmos is the absence of the eye as identified without histological examination. The first large clinical series was described by Treacher Collins,¹ and isolated cases have subsequently been reported. Recently anophthalmos and genetic microphthalmos have been considered together,² since in most cases CT scans show some remnants of either the globe or the surrounding adnexae. Anophthalmos is a rare condition that the average ophthalmologist may never see. In a prospective study of more than 50 000 pregnancies in the USA the incidence of anophthalmos or microphthalmos was found to be only 0.22 per 1000 births,³ and the prevalence among blind children was thought to be between 0.6 and 1.9%.⁴

We describe 15 cases of clinical anophthalmos seen over 16 years at the Hospital for Sick Children in Toronto. There is no clear-cut approach to treatment. A variety of surgical techniques have been tried. We outline our own experience in the management of this condition.

Patients and methods

Fifteen patients (10 of them boys) (Table 1) who presented at birth or shortly thereafter to the Hospital for Sick Children, Toronto, were reviewed. All of them were assessed by specialists in the departments of ophthalmology, neurosurgery, plastic surgery, genetics, and psychology.

Results

Two boys had bilateral clinical anophthalmos. One of them was a healthy, full-term, otherwise normal baby who was referred to our unit shortly after birth. A CT scan showed that both globes were absent, but there was evidence of extraocular muscles (Fig. 1). No hereditary or environmental factors could be implicated and the parents were not related. The child appeared mentally normal. The second bilateral case was a boy born with dysmorphic hands and feet and absence of the septum pellucidum. Unfortunately this patient was lost to follow-up. Six patients with unilateral clinical anophthalmos had anomalies in their existing eyes (Table 2). The two patients with iris colobomas had visual acuities of 20/20 and 20/30. The two with moderately severe microphthalmos had recorded visual acuities of 20/100. Another patient had an epibulbar dermoid cyst and an opaque cornea, and one had nystagmus; both of these patients were blind.

Ten patients had associated systemic anomalies as shown in Table 2. Five of them were also mentally retarded; of these five, all had midline facial clefts, one had hydrocephalus, and one had transsphenoidal

Table 1 Status of 15 patients (10 boys, 5 girls) with anophthalmos

Problems identified	No.
Unilateral anophthalmos	13
Bilateral anophthalmos	2
Systemic abnormalities	10
Abnormalities of existing eye	6

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Fig. 1 CT scan showing absent globes with the presence of extraocular muscle.

encephalocele. One patient had a right facial dysplasia and Klippel-Feil syndrome.

Genetic consultation was obtained in 12 cases, but no hereditary basis for the anomalies was found. Maternal rubella was a suspected factor in two patients with unilateral anophthalmos and systemic anomalies. In one other case the parents reported contact with pesticide spray during the first trimester.

The two patients with hydrocephalus and the patient with the transsphenoidal encephalocele had early surgical intervention. All patients with midline facial clefts (Fig. 2) had early and follow-up surgery, and both patients with cardiac anomalies underwent cardiac surgery.

Table 2 Congenital anomalies associated with anophthalmos in 15 patients

	No.
<i>Abnormalities of the existing eye</i>	
Iris colobomata	2
Microphthalmos	2
Opaque cornea and epibulbar dermoid	1
Nystagmus	1
<i>Associated systemic anomalies</i>	
Midline facial clefts	6
Hydrocephalus	2
Absence of septum pellucidum	1
Transsphenoidal encephalocele	1
Klippel-Feil syndrome	1
Finger and foot abnormalities	1
Ventricular septal defect	2



Fig. 2 Patient with unilateral clinical anophthalmos, hydrocephalus, midline facial cleft, and coloboma of the remaining eye.

Orbital reconstruction or socket enlargement was attempted in 14 patients. All received enlarging prosthetic fittings to stimulate growth and development of the bony orbit and adnexae. Six patients had difficulty retaining their prostheses, and four of them underwent multiple surgical procedures, including expansion of palpebral fissures, lid revision, and medial and lateral canthoplasty. Many of the procedures were performed for retention problems but appeared to result in cicatricial tissue formation of the socket up to six months after surgery (Fig. 3). Four patients with unilateral anophthalmos now aged 16 or more show a satisfactory cosmetic appearance.



Fig. 3 Patient with multiple lid revisions who continues to have retention problems.



Fig. 4 Patient with early prosthetic therapy without lid revisions and with good cosmetic result.

We believe this results from the fact that no lid revisions were undertaken and prosthetic therapy was initiated within the first year of life (Fig. 4).

Three patients underwent a three dimensional orbital bone expansion combined with prosthetic therapy. The result proved very satisfactory. Two other patients had tissue expanders in the form of synthetic expandable balloons with a reservoir (Fig. 5). This procedure proved unsuccessful in one because the balloons eventually ruptured. The other child with bilateral anophthalmos had the balloons in situ for six months. Periodically additional saline was injected into the reservoir to expand the balloons.

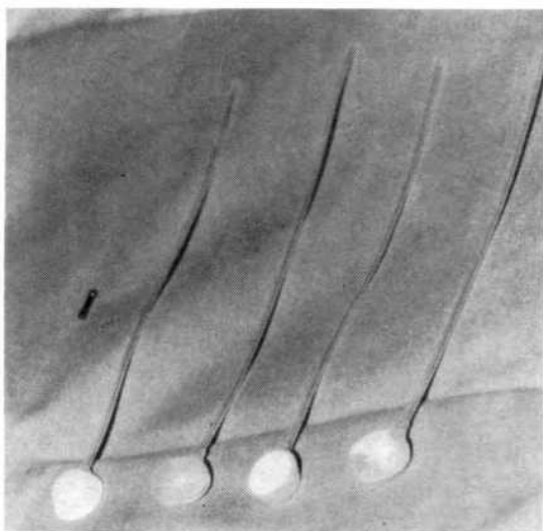


Fig. 5 Orbital balloon expanders.

Discussion

Anophthalmos is divided into primary, secondary, and consecutive types.³ In the primary type the optic primordium does not develop, but there are no generalised gross anomalies of the medullary tube. In secondary anophthalmos there is complete suppression or gross anomalous development of the entire anterior part of the neural tube. In consecutive anophthalmos the optic vesicle has formed but subsequently undergone degeneration. The primary type is thought to be bilateral and sporadic. Otherwise the child is well formed. Secondary anophthalmos results in a severely deformed child and as such does not exist in clinical practice. In the consecutive type a complete absence of the eye has been reported following histological examination in only 10 cases.⁶ The globe is also disorganised in cryptophthalmos, where there is complete failure of the eye lids. However its aetiology and its relationship with anophthalmos are obscure. More recently others have used the term microphthalmos to include anophthalmos primarily because some vestige of the globe or surrounding adnexae has developed. The validity of this term has been substantiated by orbital CT scanning. However, we use the term clinical anophthalmos as first coined by Duke-Elder² because it is appropriate to our patients.

Reported associated deformities include cranio-facial malformations, polydactyly, cardiac anomalies, and mental retardation.⁷ We found multiple associated anomalies in nine cases. In addition six patients had abnormalities in the existing eye. Two were blind and two had a visual acuity of only 20/100.

The aetiology of clinical anophthalmos has been the subject of speculation. The role of genetics has been fully discussed,⁸ and patients with autosomal dominant,⁹ autosomal recessive,¹⁰ and sex linked¹¹ patterns of inheritance have been reported. However, in most cases the problem is sporadic. In the absence of a history of disease or consanguinity an environmental cause seems probable. Anophthalmos has also been directly related to an attempted mechanical abortion⁶ and to severe maternal vitamin A deficiency.¹² In our own series two cases occurred in children with rubella syndrome.

Treatment is important to improve the cosmetic appearance, initially for the sake of the parents and later for the child. However, nine of our patients had multiple associated abnormalities. Some required life-saving surgery to treat hydrocephalus and cardiac abnormalities. Additional surgery to correct midline facial clefts further complicated treatment in four cases.

The management of clinical anophthalmos is complex. It is still not certain which overall approach

provides the best cosmetic result. The obvious orbital discrepancy and unparallel growth of the normal and anophthalmic orbits present a major challenge. Stimulating the growth of the bony orbit via prosthetic therapy at an early age helps to reduce bony orbital discrepancy; however, this technique alone does not provide a satisfactory overall result. Sufficient posterior stability must be achieved to apply anterior pressure to the lids, and this cannot be achieved without surgical intervention. Our experience suggests that unnecessary surgical lid revision should be avoided, but we recommend early prosthetic fittings.

Results achieved with three dimensional orbital expansion have been encouraging.¹³ This procedure can be done when the patient is 2½ years of age and the orbital bony growth is complete. It is major surgery and requires multidisciplinary co-operation. The other procedure, involving orbital balloon expanders, has been used for some time, but we are not yet in a position to evaluate the benefit. A potential disadvantage is the inability to create posterior orbital expansion.

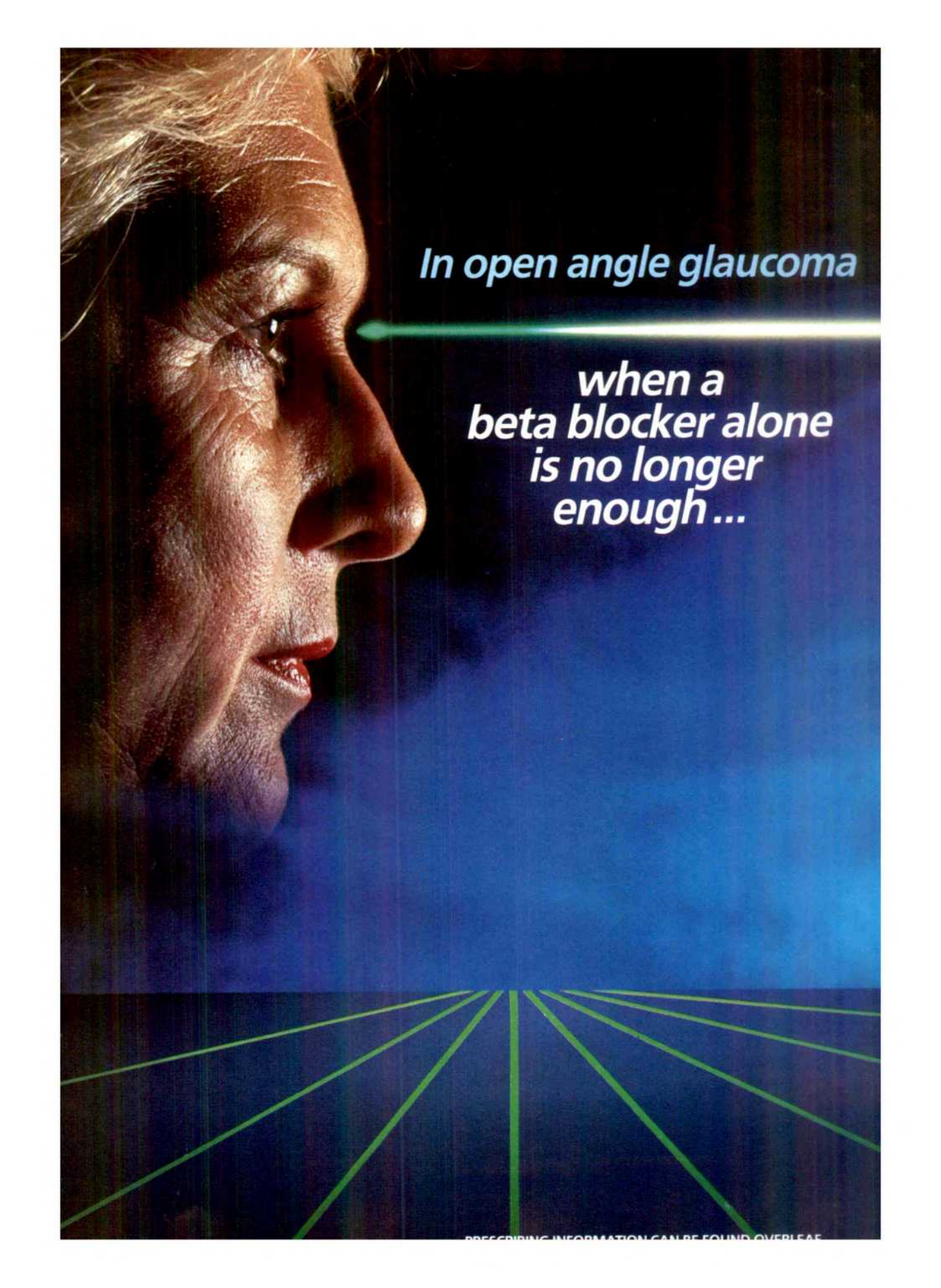
In patients with associated systemic anomalies more complex treatment is required and more time is needed to achieve an obvious cosmetic improvement. Some of them are blind or mentally retarded or both. These problems may raise questions about the wisdom of an aggressive approach. However, when the children survive, aggressive treatment can improve their quality of life and may be psychologically beneficial for the parents as well. We consider that useful rehabilitation is achieved by a multidisciplinary approach to treatment.

We thank Drs I Munro and J S Crawford for their contribution. This paper was prepared with the assistance of Elizabeth Shapter, the Medical Publications Department, the Hospital for Sick Children, Toronto, and Marese McKiernan, the Mater Private Hospital, Dublin.

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Ocular toxicity of Anandron

SIR, In studies previously published in 1983 and 1984 on treatment of prostate cancer with the combination of castration and Anandron^{1,2} two of the authors of the paper by Harnois *et al.*³ stressed the 'excellent tolerance and lack of secondary effects other than those related to hypoandrogenicity' of RU 23908 (Anandron). It is therefore surprising to read in 1986 an article by the same authors reporting a high incidence of adverse visual events, investigated in only 18 patients. No indication is given of how these 18 patients were selected among the 97 patients reported on in one of the above-mentioned articles.²

Three placebo-controlled studies of metastatic prostate cancer reported at the Second International Symposium on Cancer of the Prostate (Paris) in June 1986 did not confirm the results of Harnois *et al.* a much lower incidence of visual symptoms was noted (Table 1).

The different percentages obtained in different studies emphasise the need for double-blind placebo controls in the accurate evaluation of the incidence and severity of adverse events. Indeed visual symptoms were reported by 19% of patients in the placebo group of the Canadian study, reflecting either an environmental factor or a different approach to the adverse events questionnaire.

Among 266 patients included in non-comparative and in other double-blind trials and treated with Anandron, 300 mg per day, for periods ranging from a few days to three years (median 12 months) a total of 49 (18%) patients reported delayed dark adaptation. Three of them had to stop treatment because of this symptom. In these patients, as in those who discontinued treatment for other reasons, symptoms disappeared, as noted by Harnois *et al.* Compliance was not decreased because of this symptom, as evidenced by the small percentage of patients who discontinued treatment for this reason, and by the plasma assays of the drug performed after one to 12 months of treatment in 184 patients.⁷

The pathophysiology of this reversible impairment in dark adaptation has not been elucidated yet. It was not correlated with age, concomitant diseases (especially

cardiovascular), or other adverse events, with the exception of alcohol intolerance. The visual symptoms caused by Anandron, which require discontinuation of treatment in 1% of patients, should be weighed against its proved efficacy on metastatic bone pain, performance status, and regression of tumour mass in combination with orchidectomy, as compared with orchidectomy alone.⁴⁻⁶

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SIR, It is clear from the data presented in Table 1 accompanying the letter of Brisset *et al.* that visual symptoms occur in a relatively large proportion of patients with prostate cancer treated with Anandron. In the three studies presented 47 of 153 patients had visual problems,

Table 1 Incidence of visual symptoms in three double-blind placebo-controlled studies with Anandron

		Daily dose of Anandron		
		0 (placebo)	150 mg	300 mg
Brisset <i>et al.</i> ⁽⁴⁾	At risk (n)	50	54	54
(combined with orchidectomy)	Visual symptoms (n; %)	0 (0%)	10 (19%)	15 (28%)
Navratil <i>et al.</i> ⁽⁵⁾	At risk (n)	24	—	22
(combined with buserelin)	Visual symptoms (n; %)	0 (0%)	—	3 (14%)
Beland <i>et al.</i> ⁽⁶⁾	At risk (n)	75	—	77
(combined with orchidectomy)	Visual symptoms (n; %)	14 (19%)	—	29 (38%)

thus showing an incidence rate of 30-7%. As mentioned by the authors of that letter, the incidence of side effects depends on the content of the questionnaire and the way the necessary information is collected. In 1982, at the start of our study using Anandron, the visual symptoms noticed in a large proportion of patients were felt to be of low priority, considering the usually serious secondary effects induced by chemotherapy. In fact in the first 60 patients this secondary effect called 'snow-blindness' (or delay in the recovery of vision when going from a light to a dark environment) was reported in 80% of patients, and this information was brought to the attention of the monitor of the Anandron study.

We then realised that any side effect can become a serious problem in the treatment of prostate cancer, where it is imperative to maintain a constant level of antiandrogen in the circulation in order to block the action of androgens at all times. Any lack of compliance or failure to take the drug regularly can cause the development of tumours which will become resistant to the treatment. It is difficult, especially in this category of relatively old patients, to convince all of them of the absolute need always to take the antiandrogen at the prescribed times without any interruption. It is reasonable to assume that any side effect of a drug can become a problem for compliance, especially when the pain and the other symptoms of cancer have disappeared and the patients are back to their normal activity. It is thus extremely tempting for these patients to discontinue taking a drug which has some side effects.

Following this reasoning, we have decided to change to another pure antiandrogen devoid of such visual secondary effects. The 18 patients included in our detailed study recently published¹ were chosen at random among the initial patients treated with Anandron who complained of 'snow-blindness' and were willing to follow the appropriate ophthalmology tests. The photostress recovery time, a photopic test, was higher than normal. As indicated in the letter of Brisset *et al.*, the ocular symptoms disappeared in all cases on cessation of Anandron and change to Flutamide.

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Book reviews

Ocular Therapeutics and Pharmacology. By PHILIP P. ELLIS. Pp. 362. £43.50. Blackwell: Oxford. 1985.

This is a concise book on clinical ocular pharmacology by an American author, and therefore American medications are emphasised. The book is divided into two sections but the

first can be split into two subsections as well. It is entitled ocular therapeutics and covers the clinical pharmacology of common ocular drugs and a large section on the therapy of individual diseases. The second section is entitled therapeutic agents and takes approximately one-third of the book. The text and material are clearly presented.

The first section of the book is basic but practical and well written. It would make an easy source for examination revision, quick reference for unusual drug side effects or treatment of uncommon conditions. The information is generally practical rather than academic, giving, for example, appropriate dosages of subconjunctival antibiotics. A bibliography is given after each chapter but its usefulness is limited by absence of references to it in the text. Perhaps the greatest shortfall of this section (and many other books on ocular pharmacology) is a total lack of data on intra-ocular drug concentrations and pharmacokinetics. Until clinical textbooks contain this type of information ocular pharmacology remains based on clinical experience rather than scientific knowledge. The second section lists most of the usual drugs used in clinical practice and gives their therapeutic data in a similar way to the *British National Formulary*. British readers, however, would find the *BNF* or individual data sheets more useful because these cover drugs more related to British practice but also because they contain more detail.

In summary, this is a book for the clinical ophthalmologist and is perhaps more suited to American than British practice.

D J SPALTON

Diagnostic Imaging in Ophthalmology. Eds CARLOS F GONZALEZ, MELVIN H BECKER, JOSEPH C FLANAGAN. Pp. 366. DM 398.00. Springer-Verlag: Berlin. 1986.

This is the work of multiple authorship (31 contributors) which has been written for radiologists, ophthalmologists, neurologists, neurosurgeons, plastic surgeons, and others interested in evaluation of disorders with ophthalmological signs and symptoms. The authors' design is to provide recent knowledge in this subject in ultrasonography, computerised tomography, and nuclear magnetic resonance. There are three sections to the book: the first is a discussion of the imaging techniques; the second is devoted to the role of these imaging methods in the evaluation of ophthalmic disorders; and the last deals with the radiology of ophthalmic tumours.

The book is well produced with excellent illustrations, and it is undoubtedly the most up to date work on the subject. Like most multiple author texts there is some unevenness in the contributions. The section on plain x-ray diagnosis is inadequate, simply consisting of an unqualified list of radiological signs and their known causes without illustrations. On the other hand there is an excellent chapter on the investigation of the orbit by magnetic resonance and an interesting and informative section on computerised tomography in ocular motility disorders. Best of all there is a long chapter on congenital abnormalities which must now be the definitive text on this subject.

The work achieves its objective and is recommended to librarians looking for a textbook on orbital diagnostic imaging. Individual ophthalmologists interested in the subject may find its price excessive.

G LLOYD

Photobiology of the Skin and Eye. Edited by Edward M Jackson. Pp. 152. US\$59.50. Marcel Dekker, New York. 1986.

The combination of different disciplines is held to advance knowledge much as the fusion of unrelated chromosomes is biologically advantageous. This must be the rationale which gave rise to this sparsely illustrated book. It covers general principles of photobiology, including some of the relevant radiometry; phototoxicity, photoimmunology and photoallergy, photocarcinogenesis; how to protect oneself from the sun; photochemotherapy; and something on the eye. Each chapter is written by two to four different authors, and the editor has modestly distanced himself from them. I asked myself, for example, how much greater is the UV risk to the conjunctiva than to the skin. I could work it out from the information provided but would have appreciated cross-references. The editing also allowed names to be misspelt and references left incoherent.

The eye is covered after a fashion. The mention of the elementary warning symptom of exposure to UV, namely fuzzy vision owing to lenticular and/or corneal fluorescence, escaped me. Noxious effects of light on the retina were established in man before Noell observed them in the rat, and modern scientists do not use foot-candles. Other parts of this chapter are also out of date. The notion that surgeons are going to employ research procedures to monitor ocular and visual changes in surveillance procedures is interesting but unsupported by evidence. Such strictures apart, the chapter on the eye provides a useful introduction to ocular radiation care, and the book as a whole is valuable with its bibliographies.

ROBERT WEALE

Soft Implant Lenses in Cataract Surgery. By Thomas R Mazzocco, George M Rajacich, Edward Epstein. Pp. 150. £27.15. John Wiley: Chichester, Sussex. 1986.

This is a stimulating paperback that addresses some of the problems and prospects of soft deformable intraocular lenses currently being investigated for use in small-section cataract surgery. It is a multiauthor text, with chapters discussing the chemical, physical, and biological properties of silicones and hydrogels, lens design, and experimental and clinical experiences of implantation. There are didactic chapters on extracapsular techniques and phakoemulsification. Some chapters are better and more pertinent than others, but it is an interesting book that discusses current knowledge of these new lens materials.

JONATHAN JAGGER

Documenta Ophthalmologica Proceedings Series 45. Detection and Measurement of Visual Impairment in Pre-Verbal Children. Edited by Barrie Jay. Pp. 403. £60.95. Martinus Nijhoff: Dordrecht, Netherlands. 1986.

This volume contains the collected papers presented at a workshop held in London in 1986, where ophthalmologists and visual physiologists reviewed current original work in measurement and understanding of visual function in children. It is hoped the over-long title will not be a

deterrent to its potential readership of paediatric ophthalmologists and visual physiologists, because there is much of interest here. There are 37 separate papers and the associated discussion. Five major topics are presented, namely, normal development of vision, electrophysiological tests, measurement of visual acuity, measurement of other functions (such as visual fields), and screening of preverbal children. The mixed variety of type faces throughout the volume is a detraction in the presentation unfortunately, as the heavier type gives a greater impression of emphasis. It is appreciated that the need to publish quickly gives rise to this format.

The sections on normal development of vision, the measurement of visual acuity, and screening of preverbal children are likely to be of greatest interest to ophthalmologists and comprehensively cover the current views. Preferential looking receives a great deal of attention, and there now seems to be general agreement that this test in its various styles is reliable in infants in the assessment of visual acuity. Estimation of visual fields in infants, however, remains an uncertain and inaccurate test except under research conditions.

The book provides an excellent compilation of recent papers which has much practical and theoretical information for ophthalmologists caring for children, and visual physiologists. The marrying of theory and practice is satisfactorily achieved in this volume, and it can be recommended for reading and reference.

JAMES L KENNERLEY BANKES

Eye Diseases in Hot Climates. By JOHN SANDFORD-SMITH. Pp. 240. £7.50. Wright: Bristol. 1986.

This is a most useful, practical book for general medical practitioners and eye auxiliaries working in developing countries. The text is clearly written and is supported by excellent diagrams and colour plates of common eye conditions which the general doctor and eye auxiliary are likely to encounter in third world countries. Emphasis has been placed on the commoner eye problems and on those conditions which are preventable or treatable. In particular the chapters on nutritional corneal ulceration, trachoma, and onchocerciasis show in good illustrations some of the important eye conditions which are encountered in hot climates.

In addition this book has the great advantage of being readily intelligible to many whose English level is only intermediate. The book is excellently priced. I highly recommend it as an essential part of the library of any general doctor working in developing countries, and also as a good reference book for eye auxiliaries and eye nurses who are being trained to deal with the common eye problems which cause so much unnecessary blindness in third world countries.

A FOSTER

1985 Year Book of Ophthalmology. Edited by J Terry Ernest. Pp. 306. £41.00. Blackwell: Oxford. 1985.

The latest in a long series of *Year Books* has a new and more readable format with easy reference to the source publications, and the editor, Dr J Terry Ernest, has compiled an excellent 1985 volume.

There are 14 sections with selected articles from the world's medical literature relating to important findings and innovations published during 1984, the year preceding the *1985 Year Book*. The sections cover every important aspect of ophthalmology from eyelids to basic sciences. The lay out is excellent and the abbreviated original articles mostly read well and provide a stimulus to refer to original articles. Not surprisingly the greatest number of articles referred to are in the sections on retina and glaucoma and the fewest under vitreous. Refractive surgery covers some well balanced articles, and the editor has done well in general to produce an even emphasis throughout the *Year Book*.

It is only after a series of stretching decisions that an editor is led to select articles for inclusion in a review of the world's ophthalmological literature as in the *Year Book*. The *1985 Year Book* is an even and very readable selection of the more innovative articles and is highly recommended for all ophthalmologists. It is a pleasure to have articles selected to provide a balanced review and to guide the readership to other source articles.

JAMES L KENNERLEY BANKES

Evoked Potentials. Eds. Roger Q Cracco and Ivan Bodis-Wollner. Pp. 551. £70.00. John Wiley, Sussex. 1986.

This is the third volume in the series 'Frontiers of Clinical Neuroscience'. The book comprises 49 chapters on different subjects relating to the study of evoked electrical responses recorded from the brain and spinal cord. In effect the chapters are separate papers and stand by themselves. Roger Cracco and Ivan Bodis-Wollner have drawn together many distinguished contributors, making the whole a useful review for students, clinicians, and research workers. The book is divided into eight sections dealing with basic science aspects, animal models, diagnostic uses as well as paediatric, and surgical and psychiatric applications. All types of evoked responses are considered, and the Ophthalmologist will find about 15 relevant chapters. Applications of the VEP in children are of special interest in section VII and there are two chapters on the pattern ERG earlier in the book. There is also an up-to-date review of the VEP in human albinism.

The balance of the book reflects the current state of research in the subject and the recent increase in interest in auditory, vestibular, and somatosensory responses. It certainly should be purchased by departmental libraries and those with a special interest in the subject. N R GALLOWAY

Diagnosis and Management of Ocular Motility Disorders. By JOYCE MEIN AND BRIAN HARCOURT. Pp. 367. £45.00. Blackwell, Oxford. 1986.

The authors of this book are an orthoptist and ophthalmologist, both of the greatest distinction. It fulfils a need that has long existed for a sensible, well balanced, and down to earth text which addresses the complex field of orthoptics and ocular motility. It is equally suitable as a guide to orthoptists, who will learn much from the sections on management of motility problems, and as a clear account for ophthalmologists as to exactly what all those incomprehensible things on the orthoptic report actually mean.

The book is divided into three sections. Part I concerns history taking and patient examination, including modern tests for visual function. There are also chapters on refraction, detection and measurement of the deviation, and assessment of binocular function. Section II covers principles of non-surgical and surgical management, with clear accounts of spectacles, exercises, and eyedrops, followed by a comprehensive account of the most valuable surgical procedures, with notes on complications and re-operations. The excellent illustrations in this section are the work of Bruce Noble, also a consultant ophthalmologist at Leeds.

Section III addresses the management of specific conditions in the field of ocular motility disorders, with sections on amblyopia, concomitant strabismus, microtropia, disorders of accommodation/convergence, paralytic and restrictive strabismus, supranuclear, and internuclear disorders, and nystagmus.

Overall the book fulfils its intentions admirably, is well balanced and highly readable, and has an excellent index. There is also a very useful 10-page bibliography. All reviewers have their quibbles, however, though mine are few. I feel unhappy about the use of the term 'paralytic' as a synonym for 'incomitant' in chapters 18 and 19. The procedure of anterior and temporal transposition of the anterior half of the superior oblique muscle (illustrated on page 169) is once more called the 'Harada-Ito procedure' rather than the Fells's modification of that operation. The section on botulinum toxin injection for squint is perhaps a little lukewarm, and the dosage of toxin advocated seems rather on the high side. In every other respect I can warmly recommend this book. It should be in every resident and orthoptic library and should remain popular for many years to come.

J P LEE

Techniques in Ophthalmic Plastic Surgery. Edited by Ralph E. Wesley. Pp. 482. £46.00. John Wiley: Chichester. 1986.

This book could well be titled 'An anthology of ophthalmic plastic surgical techniques', because it is a collection of various surgeons' favourite contributions to the subject. It is divided into sections covering the whole field of ophthalmic plastic surgery, including general techniques, entropion, ectropion, ptosis, lid retraction, facial nerve disorders, reconstruction, cosmetic surgery, orbital and socket surgery. Nothing is too minor for inclusion, and there are for instance two chapters on meibomian cyst excisions. But there are also some major and innovative chapters such as those on calvarial bone grafting with a vascularised pedicle and different types of forehead and brow lift.

The 101 contributors are largely drawn from, and constitute about a third of the total membership of, the members of the American Society of Ophthalmic Plastic and Reconstructive Surgery. This society has moderately stringent criteria for membership, and the techniques described can therefore reasonably be expected to work well in practice. One contributor who is not a member of this society is the art editor, who is to be congratulated on co-ordinating such excellent diagrams. It is interesting to speculate that her chapter came from drawing the diagrams for one of the other contributors and wondering why he did not do the

surgery in a better way, such as she subsequently describes. Such is the way new techniques and modifications are continuously evolving and how much of this book has come to be produced.

The editor must be complimented on the magnificent way in which he has controlled the verbosity of most of the contributors. Only the essential facts required to describe techniques have been permitted, and clarity has been achieved with copious diagrams. Where different surgeons favour different techniques for achieving similar goals both techniques are included, such as mucous membrane grafting and vein grafting around Jones tubes for maintaining a conduit, and ear cartilage and sclera for preventing entropion after Cutler-Beard reconstructions. Rarely is anything included which some might feel is positively contraindicated, but the removal of an ellipse of skin for the correction of entropion and the excision of tarsus and posterior lamella of an eyelid to correct ptosis in patients with conjunctival scarring, which makes eversion of an eyelid difficult, are both techniques which must be treated with extreme caution by surgeons not very well versed in eyelid surgical techniques.

For anybody practising ophthalmic plastic surgery in either a major or minor way this book has plenty of surgical 'pearls' to offer, and I have seldom enjoyed reading a book more. It is not, however, and is not intended to be, a comprehensive textbook, and no attempt is made to describe a logical series of operations to cover the spectrum of ophthalmic plastic surgery, nor does the editor comment on or criticise the individual contributions. If the reader has a basic knowledge of ophthalmic plastic surgery, however, he will find this book very enjoyable, instructive, easy to assimilate, and in short warmly to be recommended.

RICHARD COLLIN

Ophthalmic Plastic and Reconstructive Surgery. By MARTIN HATT. Pp. 166. DM 128.00. Georg Thieme Verlag: Stuttgart. 1986.

This is an excellent short textbook of ophthalmic plastic surgery encompassing surgery of the eyelids, lacrimal apparatus, and orbit. The author states in the preface that he has selected procedures which are logical based on the aetiological pathophysiology and which have proved their value in a large number of cases. He also states that he does not attempt an all encompassing review of ophthalmic and surgical literature, and yet I have seldom read a textbook on this subject which is more extensively referenced. Although the author gives a clear opinion of his choice of operation, the reader is given every opportunity to study alternative thoughts and ideas by the very extensive, accurate, and current references which are referred to throughout the text and make this a work of considerable scholarship despite the book's deceptively small size. It certainly gives the reader an excellent base from which both to practise and to search for new treatment methods, which the author states is one of his hopes. Professor Blodi points out in the foreword that the primary function of the adnexa is the protection of the eyeball and the preservation of vision and that only the ophthalmologist is trained to keep these principles in mind. I agree wholeheartedly with this, and, contrary to the author's statement that 'only experts in the

field of ophthalmic plastic surgery should be involved in these procedures', I feel that this book constitutes a very sound base for the general ophthalmologist to practise and improve his surgery.

There are chapters on surgical anatomy, surgical principles, anaesthesia, entropion, ectropion, ptosis, lacrimal drainage, the conjunctiva, excision of lid tumours, eyelid reconstruction, the orbit, cosmetic lid surgery, and trauma. All are extensively illustrated with excellent diagrams and clinical photographs showing pre- and postoperative patients, but there are no photographs of the operations themselves. The author very much believes in the reconstruction of three eyelid layers, the skin, middle layer of orbicularis muscle, and the deep layer of tarsoconjunctiva. There are particularly good sections on haemostasis, the differences between local anaesthetics, lacrimal surgery including canalicular repair, the pathological examination of excised lid tumours, and socket reconstruction, in which the author includes his own very practical techniques for reconstructing the conjunctival fornices with a MIRA silicone hemisphere. He holds this in situ with tarsorrhaphies rather than the more usual techniques of fixation to periosteum or bone. The section on upper lid entropion is sketchy, reflecting probably the lack of Swiss patients with this problem. Certain procedures are omitted, such as the posterior approach to ptosis correction and the repair of medial canthal tendon injuries, and other procedures are not covered as fully as might be anticipated. There is a lack of didactic guidelines for the inexperienced on how much levator muscle to resect in ptosis surgery or how much to recess the lid retractors in the correction of lid retraction, though the techniques themselves are adequately described. The indications for specific operations such as are involved in eyelid reconstruction are described but not very precisely for the novice. Techniques of orbitotomies are described briefly, but it is difficult to get much benefit from a short section on orbital surgery without embarking on a much larger discussion of the diagnosis and management of orbital disease, and clearly this is contraindicated in a book of this size.

In summary, this is an excellent short textbook of ophthalmic plastic surgery which has been very well researched. There is enough detail, aided by the excellent diagrams, for anyone to perform competently a wide range of surgical procedures, and the reader is given a very good overview of the whole subject from which to progress if he so wishes.

J R O COLLIN

Contemporary Issues in Fetal and Neonatal Medicine. 2. Retinopathy of Prematurity. Eds. WILLIAM A SILVERMAN AND JOHN T FLYNN. Pp. 303. £32.50. Blackwell: Oxford. 1985.

The editors state in the preface of this book that it is not intended to be a comprehensive text on retinopathy of prematurity (ROP) but might more appropriately be subtitled 'current controversies'. There are 12 chapters including: the new International Classification, pathology, animal models, perinatal retinal vascular physiology, pathogenesis, vitamin E, surgical treatment, and the sequelae of ROP. There are also sections on the monitoring of oxygen

therapy, the epidemiology of ROP, and developmental issues of blind children.

The book is easy to read and, being aimed at the paediatrician as well as the ophthalmologist, is relatively free of jargon. Inevitably some sections are more successful than others, but generally the standard is very high and the chapters well referenced. Those interested in the problems of analysing incidence statistics (not only ROP) are advised to read the interesting chapter on epidemiology by Alberman. A section devoted to the clinical evolution of ROP would have been welcome to give a clinical feel to this difficult subject: when does ROP start, how does it progress or regress, and the signs and time course of the development of cicatricial disease? Indeed the best description of the acute lesion is contained in the section on pathology by Garner.

The ophthalmologist looking to this book for guidance on whether to perform cryotherapy on an individual infant will be disappointed: these issues have yet to be resolved, but at least here the problem is discussed in a sensible manner. Despite a few minor qualifications this book can be enthusiastically recommended. It is by far the best currently available on ROP and is excellent value.

A FIELDER

Fechner's Intraocular Lenses. By JOHN J ALPAR AND PAUL U FECHNER. Pp. 499. DM 198.00. Georg Thieme Verlag: Stuttgart. 1986.

This is a very well produced volume with some good colour photographs of intraocular lens techniques and pathology, comprehensively covering the field of intraocular lenses. The book is well up to date, inevitably covering several lens designs which are now rarely used. As with many volumes, some of the black-and-white photographs are either taken from colour slides or prints and lack quality and definition. The bibliography is excellent and especially valuable for workers researching in this field. Both authors are well known authorities, and I can thoroughly recommend this excellent volume.

J L PEARCE

Retinopathy of Prematurity: Current Concepts and Controversies. By A R MCPHERSON, H M HITTNER AND F L KRETZER. Pp. 237. £40.50. Blackwell: Oxford, 1986.

The editors prepared this work with the following aims: to review the pathogenesis of ROP, to examine the vitamin E dilemma, and survey the surgical treatment of ROP. With 11 of the 19 contributors coming from Houston, Texas, the book represents largely the views of this group. Many topics of interest to the clinician are covered, but unfortunately the content is often disappointing. For instance, the section on ophthalmic examination of the premature infant is seriously lacking in common sense. This is a pity, as a sensible review of examination methods including the hazards of pupillary dilating agents is much needed. Chapters on the medico-legal aspects of ROP, although relating to practice in the

USA, are worth reading. The sections on neonatal intensive care and anaesthetic considerations are superficial, but they have value in alerting the ophthalmologist to the multiplicity of systemic problems which these infants may suffer and have to be considered.

Seven chapters are devoted to the treatment of ROP by cryotherapy, scleral buckling, or vitrectomy, and, while interesting and at times excellent, all are written by surgical protagonists. As the role of cryotherapy has yet to be precisely defined, a contribution reviewing our present state of ignorance on this topic would have been welcome. The spindle cell hypothesis of the pathogenesis of ROP and the beneficial effect of vitamin E or selenium naturally occupy a great deal of this book. It is too early to know whether this theory will stand the test of time but it has certainly made researchers and clinicians question established ideas. Unfortunately in this book these ideas are presented dogmatically as established fact with little room for manoeuvre. Generally this is a difficult book to read, the style of writing is very obviously North American, some section headings are too long (one contains 26 words), and diagrams are often highly complex with legends to match. The reader who needs to know what the abbreviation IRBP stands for will have to consult the index as there is no indication in the text.

By far the most interesting chapter in this book is by Hittner and Kretzer on the differential diagnosis of ROP. This is a difficult and often neglected topic, and their approach is fresh and exciting, although there are some surprising omissions such as persistent hyperplastic primary vitreous. Nevertheless, this section is relevant not only to ROP but also to the study of ocular developmental defects.

This book cannot be recommended to the general ophthalmologist, but those with a particular interest in paediatric ophthalmology will find certain sections worth reading.

A FIELDER

Medical Lasers: Science and Clinical Practice. By J A S CARRUTH AND A L MCKENZIE. Pp. 269. £19.50. Adam Hilger: Bristol. 1986.

This is a most informative book written by a well-known clinician in the field of medical lasers and coauthored by a physicist who is also a laser safety officer.

The first and last chapters deal with laser history, physics, tissue interaction, and safety, and describe common surgical lasers used today and those with potential for the future. There are separate chapters on the use of lasers in different specialties, including gynaecology, dermatology, otolaryngology, surgery, and photoradiation therapy for tumours. There is a chapter on ophthalmology written by a non-ophthalmologist, which contains a number of inaccuracies, but considering the size of the book and chapter most eye topics are mentioned.

The strengths of the book are that laser physics, usually forgotten, can readily be revised, and it gives an insight into uses and possibilities for treatment in other branches in medicine.

J JAGGER

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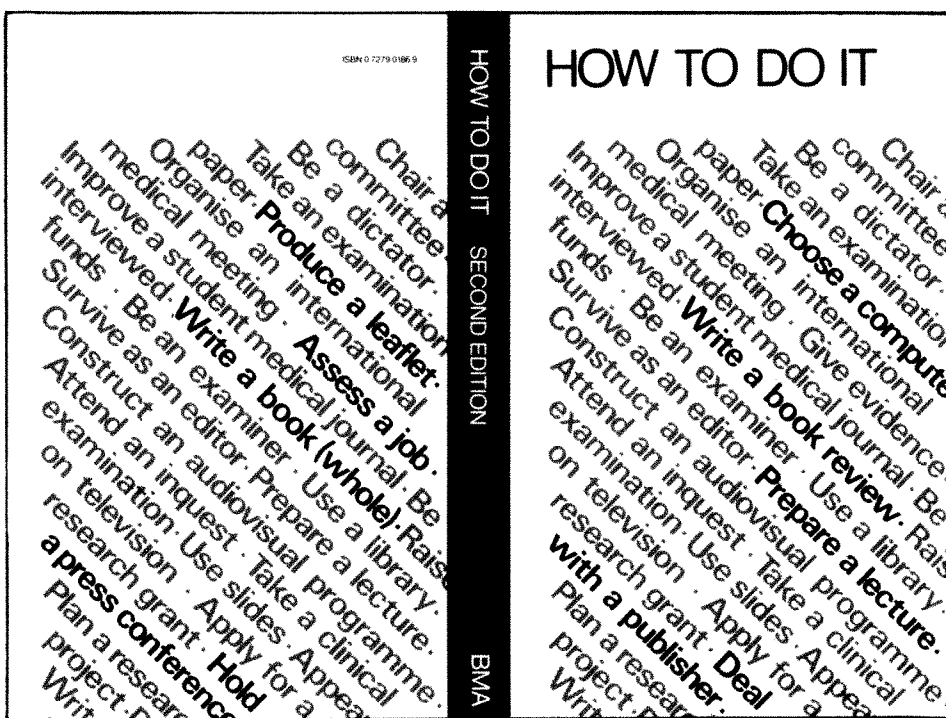
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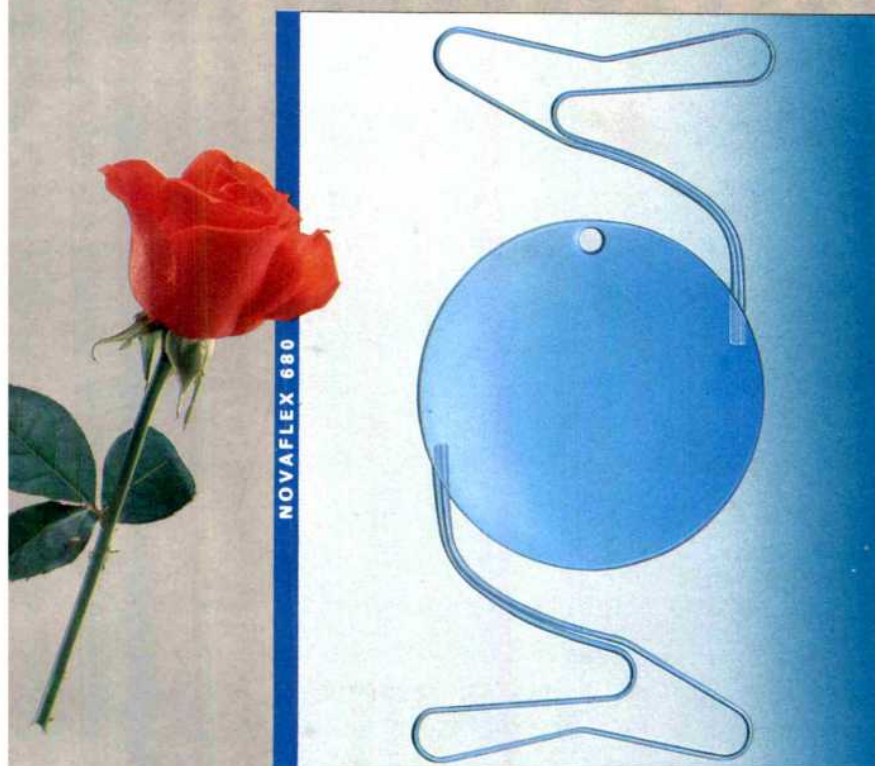
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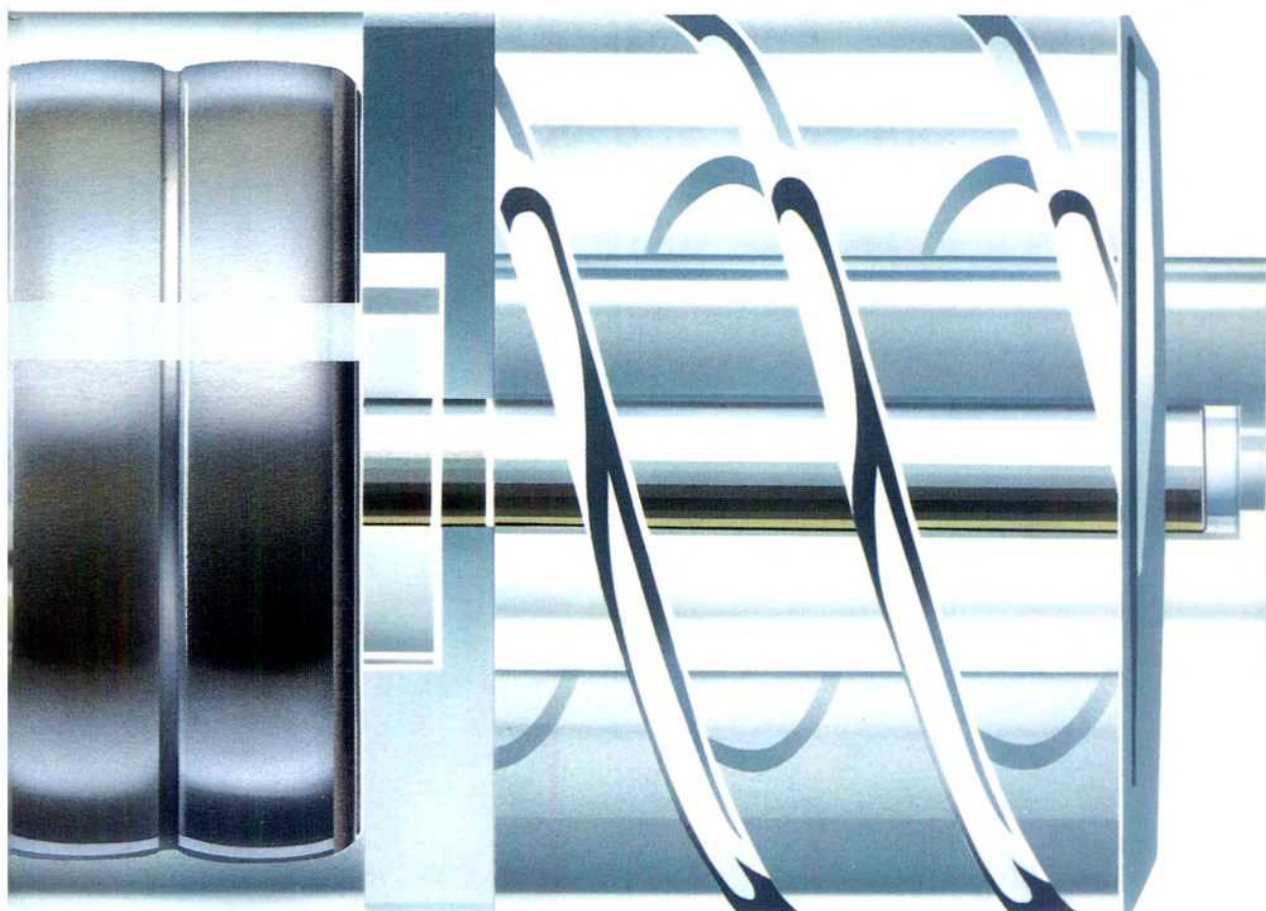
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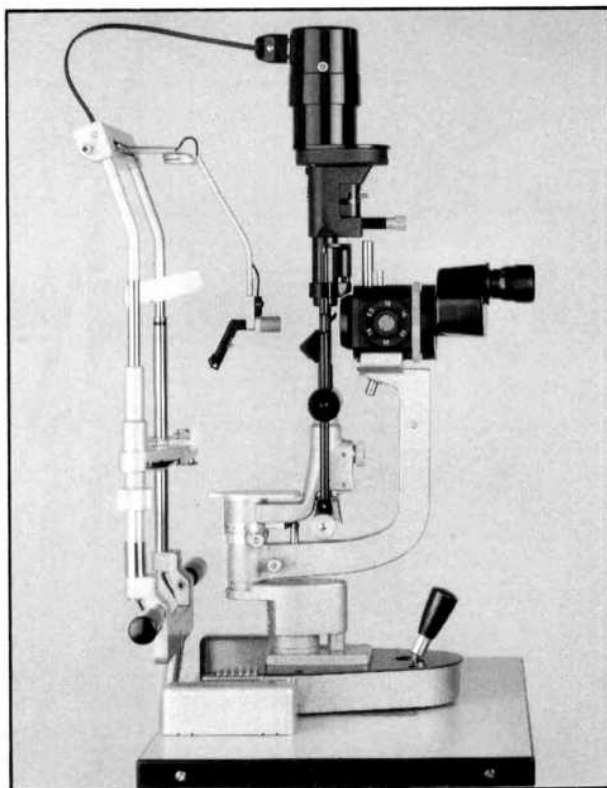
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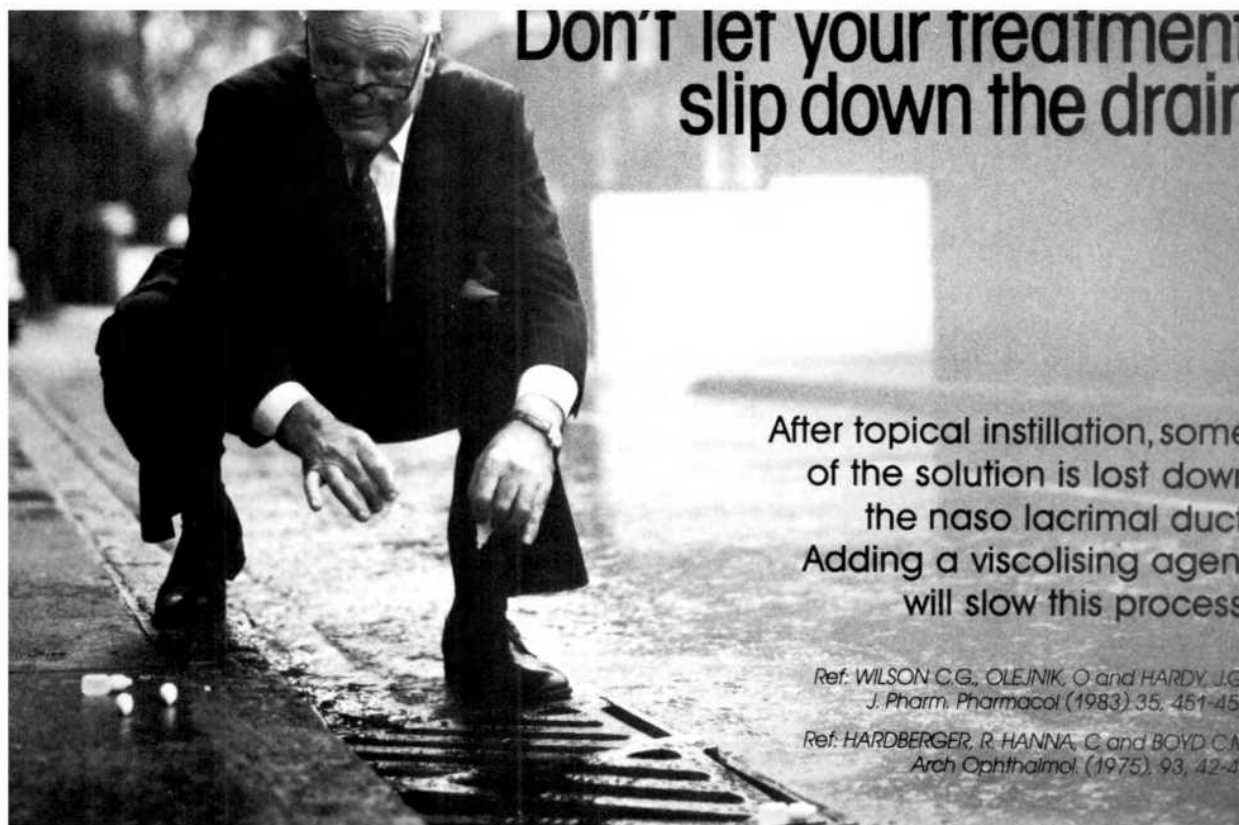
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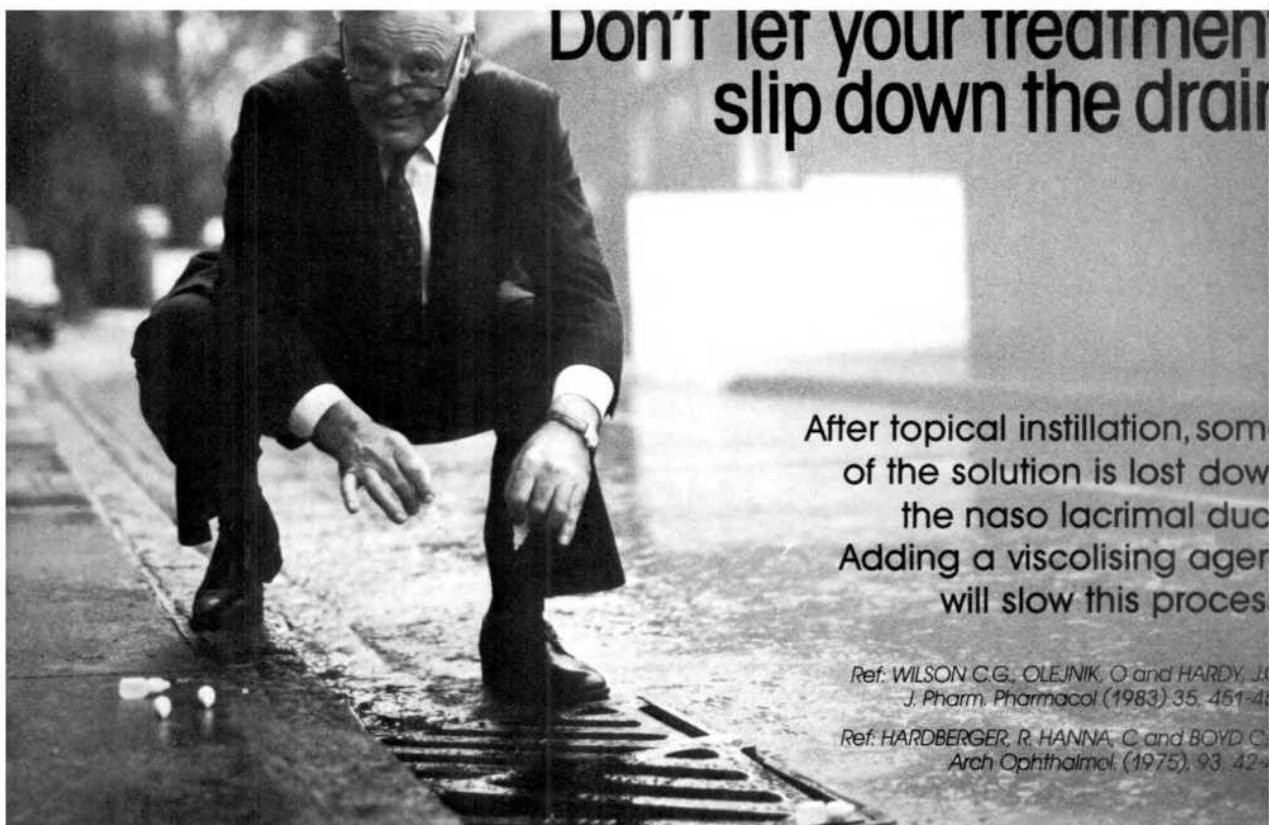
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Eyes or patients? Traps for the unwary in the statistical analysis of ophthalmological studies

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SUMMARY In reports on ophthalmological research the results of measurements on the eye are often expressed as mean and standard deviation based on m patients, n eyes ($n > m$). This approach leads to t tests that are invalid because the measurements on the two eyes of one subject are usually related, not independent. In a simulation study involving intraocular pressure data analysed in this way, the null hypothesis of no difference between groups was rejected at a nominal $\alpha = 0.05$ level in 39 out of 200 simulations; thus the true α was nearly 0.2. This approach is excessively prone to produce false positive results.

Scientific evaluation of ophthalmological interventions involves measurements of several types of variables. Typically, when beta blocking agents are evaluated for the treatment of raised intraocular pressure (IOP), interest centres on two types of measurement—those made on each eye such as the IOP, and systemic measurements such as heart rate and blood pressure. The danger that inappropriate statistical analysis may be carried out on the former type of data has prompted this investigation.

Material and methods

The data analysed were taken from a crossover study¹ comparing oral nadolol and topical timolol in 22 patients. Before any treatment was given the IOP was measured in all 44 eyes. For simplicity, consider random allocation of the 22 subjects to two treatment order groups of 11 patients each. There are 705 432 possible ways in which this can be done. Most of these will produce two subgroups of patients or eyes that are well matched for initial IOP. We would expect any valid test of the null hypothesis of equal mean IOP in these two subgroups of results—that is, initial comparability of these groups—to yield a statistically significant ($p < 0.05$) result for only 1 in 20 of these partitions.

A simulation process was carried out as follows.

The 22 subjects were allocated to two fictitious groups A and B of 11 subjects each by means of random numbers. Four ways of using an unpaired two-sample t test to compare the random groups were considered: (1) a comparison of IOP in 11 right eyes of patients in group A versus 11 right eyes of group B; (2) a comparison of IOP in 11 left eyes of patients in group A versus 11 left eyes of group B; (3) a comparison of mean IOP (average of two eyes) in 11 patients in group A versus 11 patients in group B; (4) a comparison of IOP in all 22 eyes of patients in group A versus 22 eyes in group B.

A nominal two-sided significance level of $\alpha = 0.05$ was used, so that values of $|t|$ greater than 2.086 (tests 1, 2, and 3; 20 df) of 2.018 (test 4; 42 df) were judged significant.

Results

The simulation was carried out 200 times. The four methods yielded 8, 6, 9, and 39 'significant' differences, respectively. Thus the type 1 error rates produced were 0.04, 0.03, 0.045, and 0.195.

Discussion

It is apparent that, while analytical methods 1, 2, and 3 yield appropriately low frequencies of false positive results, method 4 is excessively prone to reveal an apparent difference when all we are observing is the play of chance. The simple two-sample t test used

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assumes statistical independence of different data values. Corresponding measurements on the two eyes of one patient will not generally yield identical values, but are far from being independent.

In an actual trial t tests may appear in several contexts: an unpaired test for initial comparability between groups; a paired test to assess serial changes on one treatment; and the unpaired tests comparing period differences between random groups which constitute the analytic method of choice for the crossover trial.² The above considerations apply equally to any of these. As a general rule any significance test in which the implied total 'sample size' exceeds the number of subjects in the study is invalid. Indeed the same considerations apply to confidence intervals, and standard deviations said to be based on m patients and n eyes ($n > m$) are misleading, as they represent a mixture of between-subject and within-subject variation.

It is difficult to ascertain conclusively in which existing research publications the significance tests are invalid on these grounds. In most articles we have examined the statistical methods and results have not been stated clearly enough to enable us to tell. It is the commonly accepted standard of 'proof' that is deficient. There are other essentially similar pitfalls, such as quoting and performing significance tests based on standard deviations or standard errors derived from repeated measurements on the same eyes.

What, then, should be done? In the situation covered by our simulations, while each of the approaches 1, 2, and 3 is valid, clearly method 3 is preferable, being based on all the information in the sample, and the averaging process leads to greater precision and greater power to detect a difference of

a given size. It may happen that in some patients only one eye is used in the trial. The value for that eye may then be used instead of the average. In theory a weighted analysis is required, but it is likely to make little difference to the conclusions.

In our trial,¹ in which one of the treatments was systemic, there was only a modest gain in efficiency from using the two eyes in each subject. When both treatments to be compared are administered locally, and interest centres on local rather than systemic effects, there is an experimental design, the double-crossover (Duff G R, Graham P A, in preparation), which can yield greater statistical power. In its simplest form patients are randomly allocated to groups AB or BA. Group AB receives treatment A to the left eye and B to the right eye in the first period, then the reverse; group BA receives the treatment in the opposite order. A further refinement is possible if the main variable of interest, typically IOP, is measured on admission to the trial. Group AB can then receive treatment A to the poorer eye, B to the better in the first period, then the reverse, and conversely for group BA. Such designs are very efficient provided we have good reason to believe that there is no carry-over effect from our topical medication to the contralateral eye.

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Characterisation of ocular melanoma with cutaneous melanoma antibodies

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SUMMARY It can be difficult to distinguish between various forms of pale intraocular tumour, and in particular between an amelanotic malignant melanoma, a choroidal haemangioma, and a solitary metastasis. If a monoclonal antibody specific for melanoma could be identified, it might be radiolabelled to provide a scanning technique which could distinguish between an ocular melanoma and a similar lesion. This pilot, in vitro study was undertaken to determine if monoclonal antibody against cutaneous melanoma recognises any antigenic similarity in ocular melanomas. Three cutaneous melanoma MoAbs 225-28S, 376-96S, and 763-24T and a non-specific MoAb HMFG2 were studied. Cell impressions were obtained from fresh ocular malignant melanomas. Standard staining techniques with immunofluorescence were used. MoAb 225-28S, 376-96S, and 763-24T were positive in melanomas with a dominant epithelioid cell type and in those with a dominant spindle cell type. It is concluded that MoAb 225-28S, 376-96S, and 763-24T may be suitable for imaging ocular melanomas after labelling with ¹²⁵I, ¹¹¹In, or ^{99m}Tc.

Melanoma is the commonest primary malignancy of the eye. There are two areas of difficulty in the clinical diagnosis of the tumour in the uvea. On the one hand a small pigmented malignant melanoma may be difficult to distinguish from a benign naevus, a melanocytoma, or a carcinoma of the retinal pigment epithelium. On the other, it may not be easy to decide whether a non-pigmented mass lesion is an amelanotic melanoma, a choroidal haemangioma, or a metastasis.

Choroidal biopsy is technically possible but many small melanomas are too posterior for the procedure to be contemplated without undue risk of complications. Fluorescein angiography and ultrasound may help to strengthen the clinical diagnosis, and in centres specialising in ocular tumours some 98% of these lesions are diagnosed correctly by non-invasive investigations.^{1,2} Nevertheless it remains difficult to assess the malignant potential of some of the smaller lesions. Small melanomas can be destroyed in situ by photocoagulation or radiation with good visual results. The success of these techniques might be

more credible if confirmation of the nature of the tumour could be obtained by using a more specific imaging technique.

Recently, monoclonal antibodies (MoAb) have been used extensively in vitro and in vivo as tumour markers for diagnostic purposes. Radiolabelled MoAb have been used for diagnostic imaging of ovarian carcinomas,³ colonic carcinomas,⁴ and cutaneous melanomas.⁵ The possibility of using radiolabelled MoAb for imaging ocular melanomas remains to be explored.

This pilot, in vitro study was undertaken to determine if monoclonal antibodies against cutaneous melanoma recognise any antigenic similarity in ocular melanomas. If so they can be labelled with gamma-emitting radioisotopes like iodine-123, technetium-99m, and indium-111 and used for diagnostic imaging of ocular melanomas with an external gamma camera.

Materials and methods

Three MoAb, 225-28S, 376-96S, and 763-24T, against cutaneous melanoma were used (provided by

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Sorin Biomedica). These are IgG₂. MoAb 225-28S and 763-24T recognise high molecular weight melanoma-associated antigens (HMW-MAA) which are membrane bound and glycoprotein.⁶⁻⁸ MoAb 376-96S recognises low molecular weight melanoma-associated antigens. A non-specific MoAb against human milk fat globulin (HMFG2)¹⁰ was used as a control.

The first screening method was immunofluorescein staining on: (a) cultured ocular melanoma cell lines established from choroidal melanoma OM431 (epithelioid cell);¹¹ (b) cell impressions made from fresh ocular melanoma tumour cells obtained from six patients. Standard staining techniques were used. The MoAb were used in a concentration of 1:50 and applied to the cell impressions and frozen tissue sections. These were incubated for one hour at room temperature in a humid environment and washed gently with phosphate buffered saline (PBS) (pH 7.2). To this, antimouse rabbit antibody with fluorescein (Dako) was applied in a concentration of 1:30 and incubated for a further 30 minutes. The preparations were then washed gently with PBS, and the samples were mounted in buffered glycerol and examined under a fluorescent microscope in 495 nm excitation light.

The second method used was the avidin-biotin technique. The MoAb were applied in concentration of 1:50 on the preparations incubated for one hour at room temperature in a humid environment, and were washed gently with PBS. To this the antimouse biotinylated whole antibody (sheep) was applied in a concentration of 1:150 and incubated for 30 minutes at room temperature in a humid environment. The preparations were washed and incubated with 1:400

diluted peroxidase labelled streptavidin biotin complex (Amersham International) for 30 minutes. This was followed by a gentle wash with PBS and then incubated for 20 minutes at 37°C with 0.02% 3-amino-9-ethylcarbazol in 50 mM acetate buffer (pH 5), containing 0.3% hydrogen peroxide. The reaction was stopped by giving a gentle wash to the preparations in distilled water. The preparations were counterstained with freshly prepared Mayer's haematoxylin to achieve light staining of the samples. The preparations were then mounted in Kaiser's glycerol jelly and viewed under the light microscope. This procedure was also repeated after melanin bleaching had been carried out.¹²

Results

Cell impressions of patient 1: MoAb 376-96S and 763-24T showed a strong positive fluorescence. MoAb 225-28S showed a positive fluorescence (Fig. 1), and MoAb HMFG2 showed no fluorescence (Table 1). The histology of this specimen showed a heavily pigmented malignant melanoma of the epithelioid cell type.

Staining of cell impressions of patient 2 was negative with all the MoAb except MoAb 763-24T. MoAb 763-24T showed a doubtful positive fluorescence. The histology of this specimen showed a heavily pigmented malignant melanoma consisting of interweaving fasciculae of epithelioid and spindle B cells.

Cell impressions of patients 3 and 4: the MoAb 225-28S showed a positive fluorescence. MoAb 376-96S showed a doubtful positive fluorescence and MoAb 763-24T a positive fluorescence in patient 3,

Fig. 1 Positive immuno-fluorescence staining of cell impressions with MoAb 225-28S.

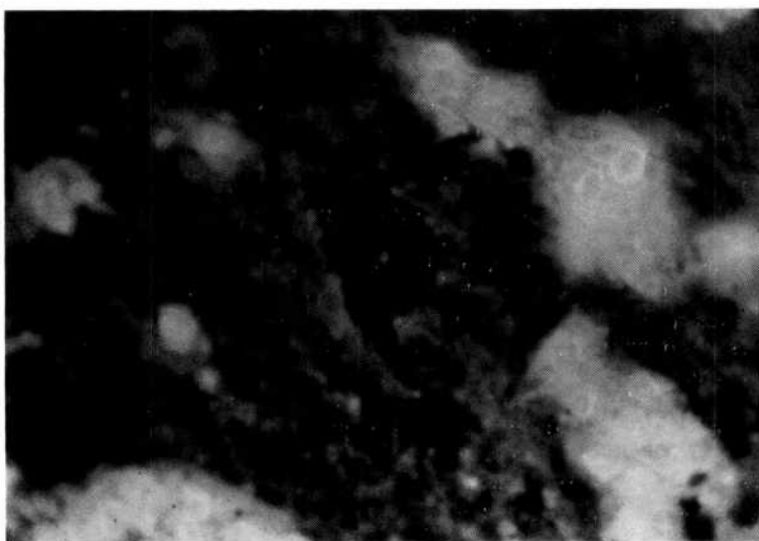


Table 1 Immunostaining responses of uveal melanoma cells

	MoAb 225		MoAb 376		MoAb 763		MoAb HMFG2	
	FR	AB	FR	AB	FR	AB	FR	AB
Cell line OM 431	+		+		±		-	
Cell impressions								
1 Epithelioid cell type	+	-	++	(-)	++	±	-	-
2 Mixed cell type	-	-	-	-	±	-	-	-
3 Mixed cell type	+	(-)	(+)	(-)	+	(-)	-	-
4 Epithelioid cell type	+	(+)	++	(+)	++	(+)	-	-
5 Spindle cell type	+	(-)	+	(+)	+	(+)	-	-
6 Mixed cell type	+	-	+	(+)	+	-	-	-

FR = Fluorescence, AB = Avidin-biotin, ++ = Strong positive, + = Positive, ± = Doubtful positive, - = Negative, () = Unreliable.

and both showed a strong positive fluorescence in patient 4. There was no fluorescence with MoAb HMFG2. Histological examination of the tumour revealed in both cases variably pigmented malignant melanomas of mixed type but with a predominance of epithelioid cells.

Cell impressions of patients 5 and 6 showed a positive fluorescence with MoAb 225-28S, 376-96S, and 763-24T. The MoAb HMFG2 was negative. Histology of both tumours showed pigmented malignant melanoma of mixed type.

The staining carried out on cultured ocular melanoma cell line OM 431 (epithelioid cell) showed a positive fluorescence with MoAb 225-28S and 376-96S a doubtful positive with MoAb 763-24T and no fluorescence with MoAb HMFG2.

The responses to monoclonal antibody with the avidin-biotin method were in several instances almost impossible to evaluate because of the melanin present in three of the tumours. Attempts to circumvent this problem by bleaching the cell impressions were unsatisfactory, since it was difficult to take the process to completion without damaging the tumour cells and causing a diffuse, non-specific peroxidase reaction. Non-specific staining of the background also added to the difficulty of interpretation.

Discussion

Cutaneous melanocytes located primarily in the epidermis are of neuroectodermal origin, whereas melanocytes of the uveal stroma appear to derive from the neural crest. This suggests that some differences as well as similarity in the antigenicity might be found, and the present limited study was undertaken to determine the extent to which monoclonal antibodies against cutaneous melanoma cells recognise the antigenically similar sites on the surface membrane of uveal malignant melanoma cells.

Testing three such antibodies on cell impressions from six different choroidal melanomas has shown that there is indeed some sharing of antigens. Five of the tumours bound all three MoAbs. A sixth tumour gave a minimal response limited to weak immunofluorescence against just one of the three antibodies, MoAb 763-24T.

These preliminary findings suggest that monoclonal antibodies to malignant melanomas of the skin, which are becoming increasingly available for clinical application, might be used to detect intraocular melanoma. There are several ways in which this potential might be exploited.

One feasible application would be distinguishing uveal melanomas from other intraocular tumours in a non-invasive manner by measuring the uptake of radiolabelled melanoma-specific antibodies. A non infrequent source of diagnostic confusion is presented by choroidal haemangiomas and by blood-borne metastases from a distant site. In this context it is relevant to inquire as to the degree of cross-reactivity for the monoclonal antibodies raised against melanoma cells to cells of other histogenesis. Precise information concerning the antibodies used in this study is not available, but others¹³⁻¹⁵ have described cross-reactivity between some monoclonal antibodies raised against human cutaneous melanoma cells and astrocytomas, medulloblastomas, and unspecified epithelial cancers. It is possible that the antibodies are recognising neuroectodermal and to some extent related neural crest differentiation antigens. Nevertheless, the risk of making a false diagnosis of uveal melanoma may be reduced by using not just one but several antibodies, since the degree of antigen sharing is not complete.

Differentiation between malignant and benign pigmented lesions within the eye can be another source of difficulty. The binding of monoclonal antibodies against skin melanomas to uveal naevi has yet to be tested, but a study by Seeger and

coworkers¹⁵ suggests that some uptake might be expected. The same study did demonstrate, however, that malignant melanoma cells have a significantly greater avidity for antibody than do normal melanocytes.¹⁵ It may be necessary, therefore, to distinguish malignant lesions from naevi by quantitative refinement of the scanning techniques.

Use is already made of radiolabelled monoclonal antibodies¹⁶ to image metastases of skin melanomas at distant sites, and, given the sharing of tumour associated antigens, the same approach can be used to identify metastasis of uveal melanoma. This could be a major clinical application of the monoclonal antibodies.

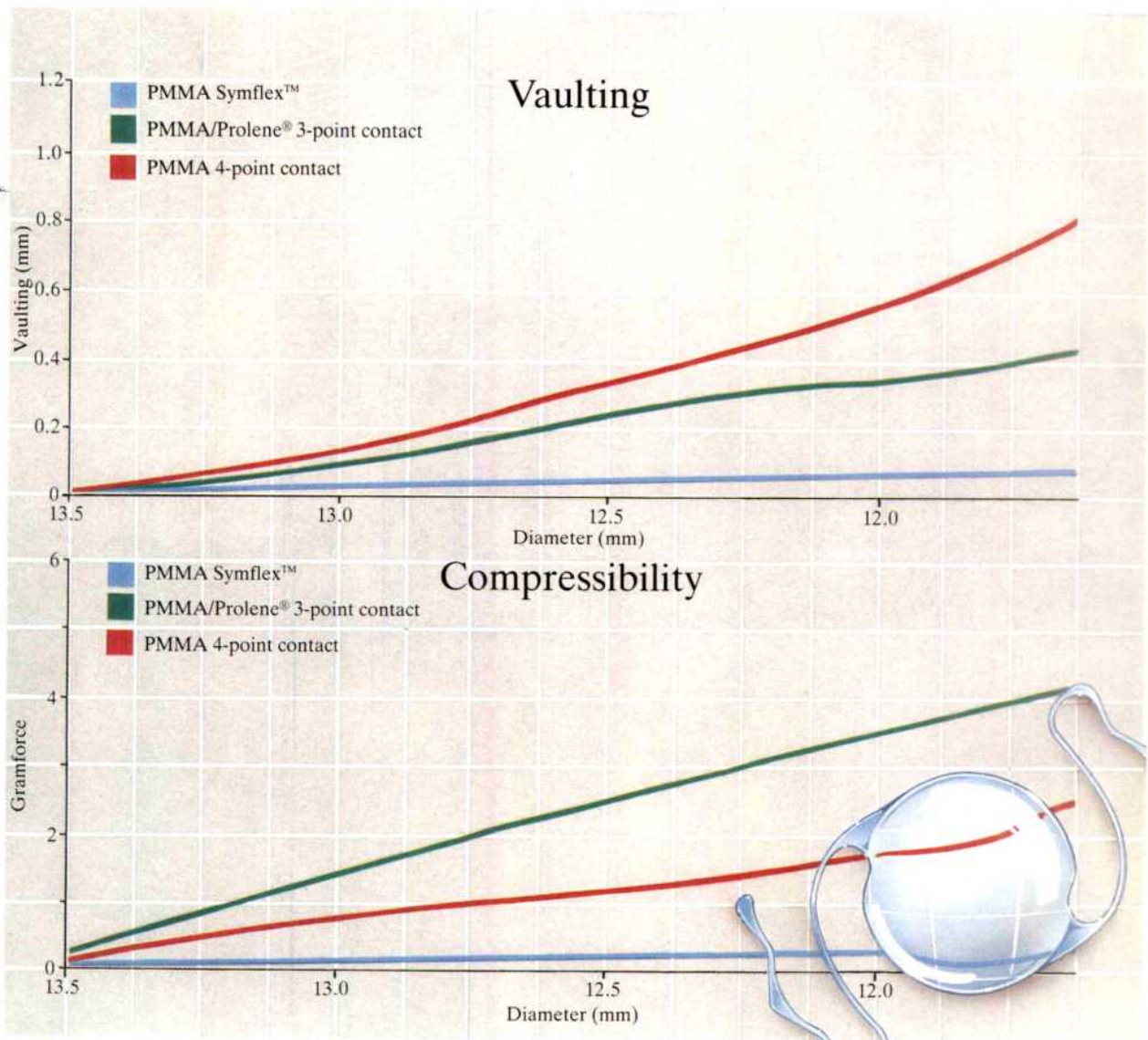
Monoclonal antibodies of the type described could also be of value in histological diagnosis if combined with an immunofluorescent or immunoperoxidase technique. As such they would be particularly relevant to the differential diagnosis of nonpigmented spindle cell tumours in the eye.

We thank Sorin Biomedica company for providing the antibodies for this project and Professor Scassallati for his help and advice. We acknowledge the support of Imperial Cancer Research Fund (Mr JL Hungerford and Dr M Granowska) and the Joint Research Board of St Bartholomew's Hospital (Dr J Bomanji).

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Reference 1. Kralian LM. American Journal of Optometry and Physiological Optics 1986; 63 (No. 4): 304-308.

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Radioimmunoscintigraphy of ocular melanoma with ^{99m}Tc labelled cutaneous melanoma antibody fragments

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SUMMARY The possibility of using radiolabelled monoclonal antibody fragments to image uveal melanomas has been assessed in a pilot study. ^{99m}Tc labelled F(ab')₂ fragments of MoAb 225.28S raised against cutaneous melanomas were used. Initially 10 patients were imaged. In five patients the clinical findings were typical of uveal melanoma. Immunoscintigraphy was positive in all five cases. In a further five patients there was doubt about the diagnosis. One was thought to have a choroidal haemangioma but failed to respond to treatment and immunoscintigraphy was positive, suggesting a diagnosis of melanoma. Two patients were assigned a diagnosis of choroidal haemangioma, one of melanocytoma or possible retinal pigment epithelium carcinoma, and one of metastasis. Immunoscintigraphy was negative in all these four cases. In combination with established diagnostic tests immunoscintigraphy may have a part to play in differentiating uveal melanoma from other similar tumours.

Malignant melanoma is the most frequently encountered primary intraocular neoplasm. Improved standards of eye care have resulted in more frequent discovery of asymptomatic lesions. These can be detected so early in their natural history that it may be difficult to distinguish between a small melanoma and a large choroidal naevus. A small symptomatic melanoma in turn may be similar in appearance to a choroidal haemangioma or a choroidal metastasis, particularly when relatively amelanotic. Because of the hazards of biopsy within the eye the ophthalmologist must differentiate between these lesions on clinical grounds aided by special investigations.

At present both radical and conservative options for treatment of uveal malignant melanoma rest largely on a clinical diagnosis. When the radical option is exercised or when a melanoma is treated by local excision, a tissue diagnosis is obtained, albeit retrospectively. On the other hand when an ocular melanoma is treated conservatively by photocoagulation or radiation, a tissue diagnosis may never be obtained.

Although radioactive tracers have been used since 1952¹ to localise choroidal melanomas, no single nuclear imaging test has helped to answer these diagnostic problems specifically. The ^{32}P test has been used extensively in this context,^{2,3} but the limitations of this test have restricted its popularity.⁴⁻⁸ The test is more accurate for large tumours, for which the diagnosis is rarely in doubt, than for small lesions which may be difficult to diagnose. The short range in tissue of beta particles emitted by ^{32}P means that a surgical operation is required to place the probe over the tumour and over an unaffected area of the choroid for comparison. Several preclinical studies have identified other radiopharmaceuticals as likely agents to localise melanomas.⁹ Agents with melanin affinity—for example, quinolines,¹⁰ melanin precursors such as thiouracil,^{11,12} and non-specific tumour localising agents such as gallium¹³—have been evaluated and have had limited success.

Nuclear medicine has added a new dimension for localising tumours in the last decade by means of radiolabelled monoclonal antibodies (MoAb) against tumour associated antigens for diagnostic and therapeutic purposes.¹⁴ This study follows preliminary in-vitro work with monoclonal antibodies (MoAb) raised against cutaneous melanoma to recognise

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antigenic similarity in ocular melanomas.¹⁵ The results were sufficiently encouraging to proceed to the use of these antibodies *in vivo*. It has been established that $F(ab')_2$ fragments are more effective for radioimmunodetection than whole MoAb, since non-specific uptake by the spleen, liver, and bone marrow is reduced and they are more rapidly cleared from the blood.¹⁶ Comparative studies on biodistribution of $F(ab')_2$ fragments with different radioisotopes (¹³¹I, ¹²⁵I, ¹¹¹In, and ^{99m}Tc) indicate that ^{99m}Tc- $F(ab')_2$ fragments are the most suitable for radioimmunoscintigraphy when there is rapid tumour uptake, because of the high signal generated from the target through the injection of a high activity short-lived radionuclide (half life of 6 h). ^{99m}Tc is also readily available, cheap, and has favourable dosimetric consideration.¹⁷ Based on these parameters it was decided to use ^{99m}Tc labelled $F(ab')_2$ fragments of MoAb 225.28S (provided by Sorin Biomedica) for the initial work.

Materials and methods

PATIENTS

Ten patients were studied serially. Five patients had a known primary uveal melanoma, and five had a doubtful clinical diagnosis of melanoma. The study has been accepted by the City and Hackney District Ethical Committee.

RADIOLABELLING

The antibody was provided in the form of an instant labelling kit Technemab-K-1 of Sorin Biomedica. Labelling was carried out by the addition of sterile ^{99m}Tc pertechnetate to a lyophilised preparation containing 350 µg of $F(ab')_2$ fragments of MoAb 225.28S, which is against a high molecular weight-melanoma associated antigen (HMW-MAA). After thorough mixing the solution was incubated for 15 minutes at room temperature. Free ^{99m}Tc was then removed by ion exchange column chromatography through sterile pyrogen free DEAE-Sephadex A25. This method gave 85–90% labelling, and residual free ^{99m}Tc was <5%. The labelled preparation was injected within one hour of being prepared.

IMAGING PROTOCOL

Prior to the study the procedure was explained to the patient and written informed consent obtained in each case. Before the intravenous injection of labelled antibodies the patient's skin was tested for hypersensitivity to mouse immunoglobulins. No reaction was noted in any patient. 400 mg of potassium perchlorate was given orally 30 minutes prior to the injection to block the thyroid. A large field of view gamma camera (GE 400AT) with a

general purpose collimator and an on-line computer (DEC Gamma 11) was used. The patient was placed supine with head fixed in a foam support. The camera was placed over the head in the anterior Waters view (caudal tilt of 15–30°). This position was chosen for the head to optimise separation of the orbits from interfering background, such as the nasal cavity and paranasal sinuses. An 18 gauge cannula was placed in an antecubital vein connected to a three-way stopcock. Between 340 and 370 MBq of ^{99m}Tc $F(ab')_2$ was placed through the three-way stopcock and flushed with 20 ml of 0.9% normal saline. Dynamic images were acquired on a 64×64 matrix on the computer at a frame rate of 1 second/frame for 60 frames followed by 30 s/frame for 18 frames with the camera placed over the head in the anterior Waters view. Static images were acquired on a 128×128 matrix on the computer with the camera over the head, chest, and pelvis for 400 000 counts each at 20 minutes, 1 h, 3 h, 5 h, and 6 h.

Results

Patient 1 was a 57-year-old white male with a large inferolateral choroidal malignant melanoma in the right eye measuring 18 mm in maximum diameter and 11 mm in thickness on ultrasound. Immunoscintigraphy was positive (Figs. 1a, 2). The eye was subsequently enucleated and histopathology



Fig. 1a

Fig. 1 Immunoscintigraphy images at 5 h. (T)=Tumour. (a) Choroidal melanoma right eye. (b) Haemangioma right eye. (c) Melanocytoma right eye.



Fig. 1b



Fig. 1c

revealed a lightly pigmented, vascular, predominantly spindle cell malignant melanoma.

Patient 2 was a 35-year-old Asian male with a large ciliochoroidal melanoma in his right eye measuring 13 mm in maximum diameter and 9 mm in thickness and situated temporally. Immunoscintigraphy was strongly positive for the right eye but was also weakly so for the left (Table 1). The right eye was enucleated, and histopathology of the specimen

showed a heavily pigmented, mixed cell melanoma arising in the ciliary body. The patient had heavily pigmented fundi, but a possible flat choroidal naevus was identified in the left eye.

Patient 3 was a 43-year-old white female with a small, lightly pigmented malignant melanoma measuring 7 mm in maximum diameter and 3 mm in thickness and situated above the left macula. Growth of the lesion had been recorded photographically.

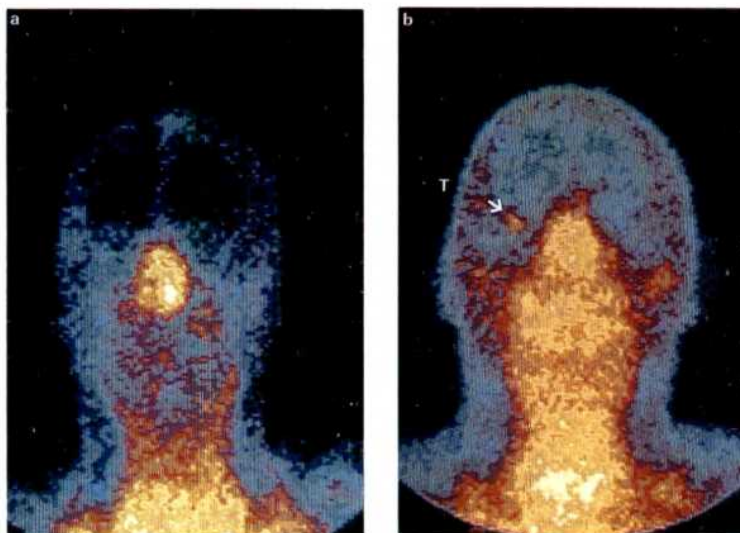


Fig. 2 Immunoscintigraphy images of patient 1. (T)= Tumour. (a) Static image at 20 minutes. (b) Static image at 6 h.

Table 1 Clinical and immunoscintigraphy data

Patient no	age	Clinical diagnosis	Immunoscintigraphy			
			Dynamic		Static	
			L	R	L	R
1	57	Melanoma R eye	-ve	-ve	-ve	+ve
2	35	Melanoma R eye	-ve	-ve	+ve	+ve
3	43	Melanoma L eye	-ve	-ve	+ve	-ve
4	34	Melanoma L eye	-ve	-ve	+ve	-ve
5	27	Melanoma R eye	-ve	-ve	-ve	+ve
6	35	Melanoma R eye	-ve	-ve	-ve	+ve
7	69	Haemangioma R eye	-ve	+ve	-ve	-ve
8	50	Melanocytoma R eye	-ve	-ve	-ve	-ve
9	53	Haemangioma L eye	-ve	-ve	-ve	-ve
10	45	Metastasis R eye	-ve	-ve	-ve	-ve

Immunoscintigraphy was positive, and the tumour was treated conservatively with a ^{106}Ru scleral plaque.

Patient 4 was a 34-year-old Asian female with a large ciliary body malignant melanoma invading the iris root nasally in the left eye. The tumour measured 12 mm in maximum diameter and 6 mm in thickness. Immunoscintigraphy was positive. Enucleation was advised but was refused. The patient was treated with ^{106}Ru plaque but enucleation was once more advocated for extrascleral extension and persistent glaucoma. Histopathology of the enucleated eye confirmed the presence of a heavily pigmented totally necrotic melanoma arising in the ciliary body.

Patient 5 was a 27-year-old Asian female with a large ciliochoroidal malignant melanoma situated temporally in the right eye and associated with a total serous retinal detachment. The tumour measured 18 mm in maximum diameter and 12 mm in thickness. Immunoscintigraphy was strongly positive. The right eye was enucleated. Histopathology of the enucleated eye revealed a pigmented, vascular, predominantly spindle cell malignant melanoma.

Patient 6 was a 35-year-old white male with a small non-pigmented mass superotemporal to the right macula and measuring 6 mm in maximum diameter and 3 mm in thickness. There was an extensive associated serous retinal detachment. The patient was in good health, and comprehensive systemic examination revealed no evidence of tumour elsewhere. Ultrasound and fluorescein fundus angiography were equivocal for choroidal melanoma or haemangioma. There was a family history of cutaneous haemangioma, and a tentative diagnosis of choroidal haemangioma was made. Neither laser photocoagulation nor subsequent lens sparing treatment with external beam radiotherapy to a dose of 15 Gy resulted in resorption of subretinal fluid. Immunoscintigraphy became available and was positive. The diagnosis was revised to choroidal

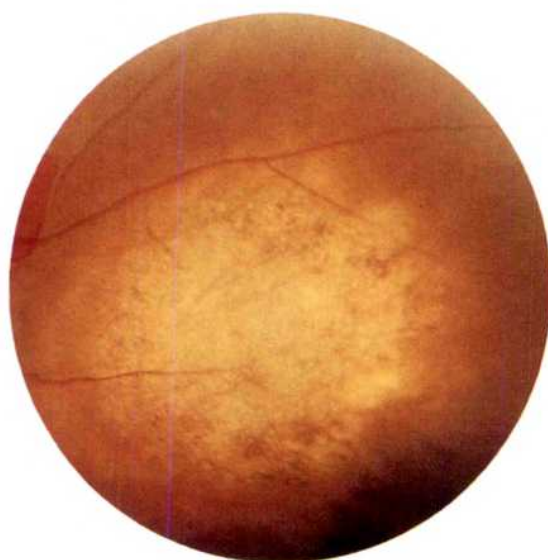


Fig. 3 *Patient 7. Non-pigmented choroidal mass nasal to the right optic disc.*

melanoma and conservative treatment was undertaken with ^{106}Ru scleral plaque.

Patient 7 was a 69-year-old white female with a non-pigmented mass nasal to the right optic disc considered by the referring ophthalmologist to be an amelanotic malignant melanoma (Fig. 3). The lesion measured 7 mm in maximum diameter and 2 mm in thickness on ultrasound. Fluorescein angiography showed very early, uniform (Fig. 4a), and subsequently intense (Fig. 4b) choroidal filling which was more suggestive of a choroidal haemangioma. Immunoscintigraphy showed a vascular blush in the involved eye on the initial dynamic images but the static images were negative (Fig. 1b). The diagnosis was revised to choroidal haemangioma, and treatment by laser photocoagulation was instituted.

Patient 8 was a 70-year-old white female with an extremely heavily pigmented mass arising just above and partially obscuring the right optic disc (Fig. 5). The maximum diameter of the lesion was 12 mm and it was 6 mm thick. Ultrasound also suggested that there was superficial invasion of the optic nerve. The differential diagnosis was considered to be between a melanocytoma, a juxtapapillary melanoma, and a carcinoma of the retinal pigment epithelium. Immunoscintigraphy was negative (Fig. 1c), and management was by serial observation with photography and ultrasound.

Patient 9 was a 53-year-old white male with a pale lesion at the superior margin of the left optic disc (Fig. 6). The tumour measured 9 mm in maximum diameter by 2 mm in thickness. Fluorescein fundus

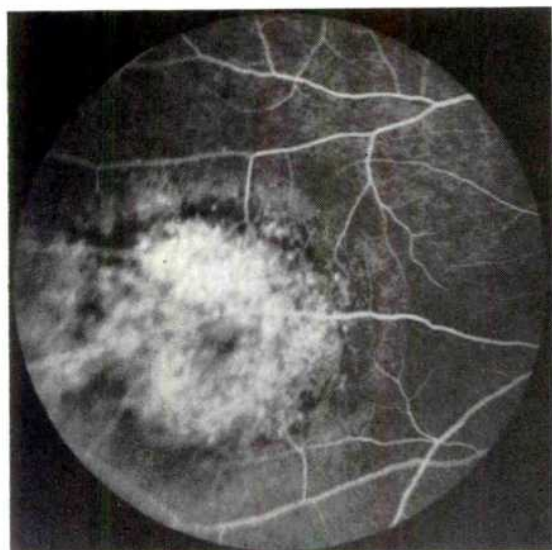


Fig. 4a

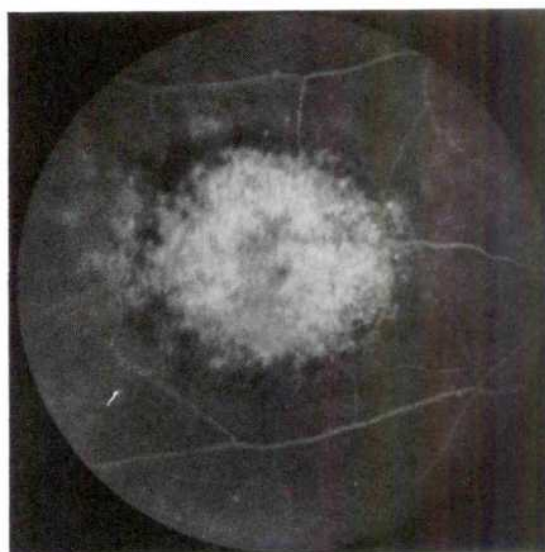


Fig. 4b

Fig. 4 Patient 7. (a) Arteriovenous phase fluorescein angiography. (b) Late venous phase fluorescein angiography.

angiography was equivocal for a choroidal haemangioma or a melanoma. Immunoscintigraphy was negative. A diagnosis of choroidal haemangioma was made. There was no associated serous retinal detachment, and management was by serial observation with photography and ultrasound.

Patient 10 was a 45-year-old white male with a pale lesion immediately temporal to the right macula

measuring 7 mm in maximum diameter and 3 mm in thickness (Fig. 7). Fluorescein angiography was atypical of a choroidal haemangioma and the differential diagnosis lay between an amelanotic melanoma and a metastasis. Immunoscintigraphy was negative (Fig. 8). The patient, a non-smoker, was clinically well, but a small opacity was seen at the right hilum on plain chest x-ray, and subsequently a

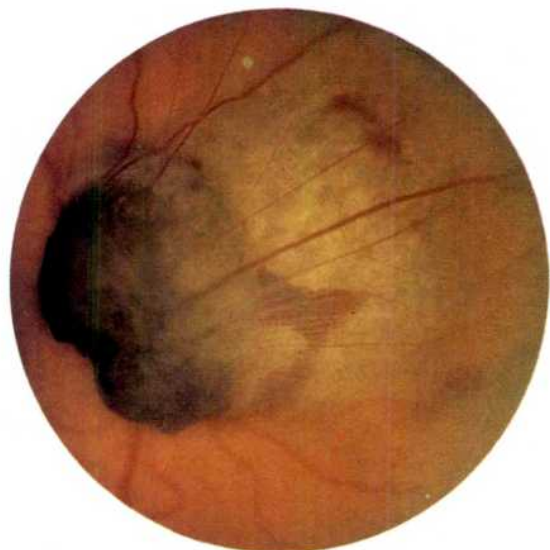


Fig. 5 Patient 8. Heavily pigmented mass arising just above and partially obscuring the right optic disc.

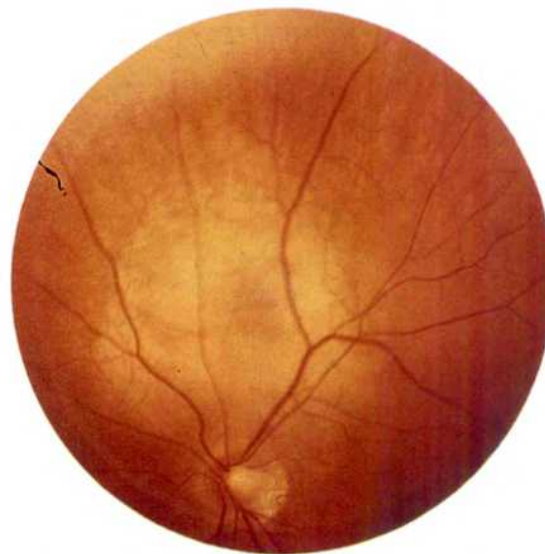


Fig. 6 Patient 9. Pale choroidal mass superior to the left optic disc.

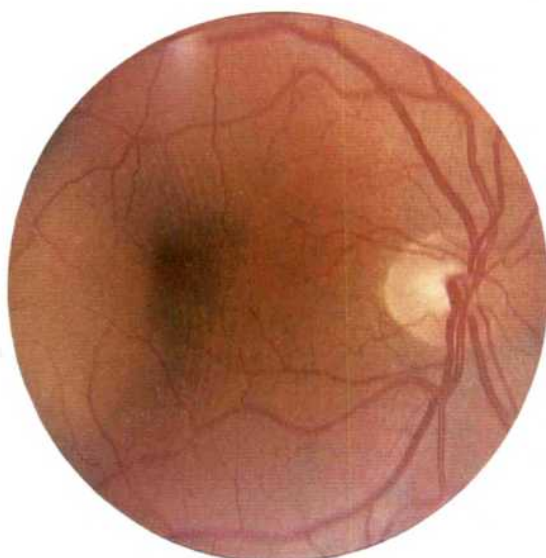


Fig. 7 Patient 10. Pale choroidal mass temporal to the right macula.

cystic lesion was demonstrated on CT. Bronchoscopic biopsy showed an adenocarcinoma.

The best scintigraphic images for tumour detection were obtained between 3 h and 6 h after injection (Fig. 2b); during this time interval the tumour/background ratio was highest. In some cases the tumour was visualised at 1 h after injection. The nasal cavity, heart, liver, kidneys, and bladder were visualised in all cases on the static images. In three patients

some splenic uptake were also noted. Maximum uptake was seen in the kidneys. In two cases, patients 1 and 4, cell impressions of the resected tumour were obtained. These were subjected to immunofluorescence staining; both specimens also gave a strong positive immunofluorescence with MoAb 225.28S *in vitro*.

Discussion

The HMW-MAA is a combination of two non-covalently associated glycopolypeptides. One has an apparent molecular weight of 280 K; the other is composed of a heterogeneous array of glycopolypeptides with molecular weights ranging from 300 K to 700 K.¹⁸⁻²¹ The HMW-MAA has not been detected in normal tissues except for clusters of Malpighian cells in epidermis and hair bulbs.²¹⁻²² Although the HMW-MAA carries the determinants for more than one MoAb, a subpopulation of HMW-MAA expresses only the determinant defined by MoAb 225.28S, and this subpopulation is present in primary and metastatic melanomas and benign skin naevi.²³ The results of imaging cutaneous melanomas in 43 patients with F(ab')₂ MoAb 225.28S indicate that this technique has a sensitivity of 77% and a specificity of 99%.²⁴

The use of an antibody raised against cutaneous melanoma for imaging ocular melanomas is potentially specific. It has been shown that the ocular melanomas have some similarity to the cutaneous melanomas in their antigenic features.¹⁵ This sharing of antigenicity can be used for diagnostic purposes.

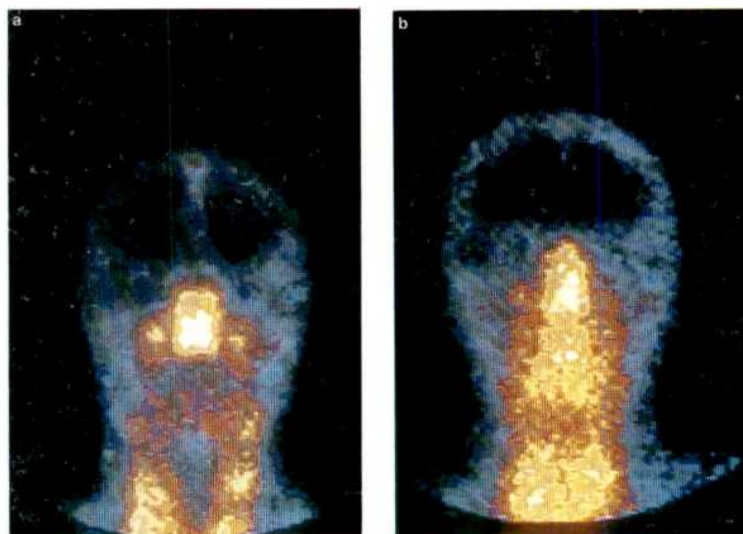


Fig. 8 Immunoscintigraphy images of patient 10. (a) Static image at 20 minutes. (b) Static image at 6 h.

This small series covers some of the puzzling cases which present to the ophthalmic surgeon as a diagnostic dilemma, and it is considered that this technique has complemented other diagnostic methods in this context. A major problem is to differentiate a choroidal melanoma from a choroidal haemangioma. In the case of ocular melanoma this is achieved when a focal area of increased uptake is seen to develop with time, whereas a haemangioma shows an early blush decreasing with time. It is not yet clear whether a negative scan rules out the diagnosis of melanoma. Serial image subtraction, image enhancement techniques, and kinetic analysis with probability mapping^{25,26} are expected to allow even smaller ocular melanomas to be detected.

Another possible application of this imaging method would be for imaging metastatic lesions from ocular melanomas. Because there is high uptake in the kidneys which interferes with the image a small metastasis in an area of the liver overlying the kidney would be missed. But metastases at other sites should be detected. At this stage only ^{99m}Tc F(ab')₂ fragments of the MoAb 225.28S have been evaluated. In-vitro staining characteristics of this antibody were less marked when compared with MoAb 763.24T and 376.96S.¹⁵ Whether these other antibodies or their fragments labelled with ^{99m}Tc or ^{125}I would also improve the image remains to be explored.

The specificity for radioimmunoscinigraphy procedures as a whole is high. However, the sensitivity varies in accordance with the tumour size, lesion site, and the rate and amount of antibody uptake. In this study we had one false positive result in patient 2. This may have resulted from the presence of a naevus in the second eye, and the immunoscinigraphic response of the choroidal naevi remains to be investigated. As with any diagnostic imaging test for tumours, the possibility of a false negative or false positive result is always present, but it is hoped that this test will ultimately supplement and complement other established diagnostic tests and help the ophthalmic surgeon in the management of patients with ocular tumours.

We thank Sorin Biomedica company for providing the antibodies for this project and Professor G A Scassallati for his help and advice in this project. We also thank Mr K Solanki for helping with the radiolabelling and the staff of nuclear medicine for their help. We acknowledge the support of Imperial Cancer Research Fund for Mr J L Hungerford and Dr M Granowska. We are grateful to the St Bartholomew's Hospital Joint Research Board for the use of the facilities of the St Bartholomew's Hospital Centre.

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Cytological factors relating to posterior capsule opacification following cataract surgery

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G M THOMPSON²

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SUMMARY Simulated extracapsular cataract extractions on cadaver eyes were performed which demonstrated that the cells of the anterior capsule remain largely intact and that only a small amount of cortical lens matter remains postoperatively. Human lens epithelial cells from normal and cataractous lenses were grown in culture. There was no appreciable difference in growth rate between cells from normal and those from cataractous lenses or between equatorial and central capsule cells. The cells grew from the cut edges of the capsule, suggesting that release from contact inhibition is an important factor in stimulating proliferation. The daughter cells became increasingly abnormal and metaplastic in successive generations, but there was no evidence of differentiation into fibroblasts within the 35-day culture period, suggesting that a retinal growth factor may be involved with the fibrosis occurring in opacification of the posterior capsule. A small anterior capsulotomy will release fewer cells from contact inhibition and hence reduce cell proliferation after extracapsular cataract extraction.

The resurgence of the extracapsular technique of cataract extraction has been accompanied by a corresponding increase in the prevalence of post-operative posterior capsule opacification.¹ The effectiveness of a cataract extraction, with or without an intraocular lens, may be considerably reduced when severe opacification occurs. Although the capsule membrane may be ruptured by YAG laser capsulotomy,^{2,3} this is a second procedure that is associated with further complications and may be difficult in elderly patients. If a greater understanding of the mechanisms underlying opacification of the posterior capsule could lead to its decreased incidence, there would be considerable clinical benefit.

Our study was in two parts: firstly, we obtained enucleated human eyes and performed an extracapsular lens extraction under operating theatre conditions. These eyes were examined histologically in order to determine which elements of the lens remained after an, apparently, complete extracapsular lens extraction.

Secondly we obtained normal and cataractous human lenses and examined the growth of the epithelial cells in cell culture in order to determine the best type of capsulotomy in extracapsular surgery. In particular: (a) The pattern of growth from capsule edges; whether removal of intercell contact inhibition is a factor in stimulating epithelial proliferation. (b) Whether cells from different parts of the capsule grow at different rates – in other words, does the site of the capsulotomy influence epithelial cell proliferation? (c) Whether epithelial cells from cataractous lenses grow at a different rate from those of normal lenses.

Material and methods

SIMULATED EXTRACAPSULAR CATARACT EXTRACTION

An extracapsular lens extraction was performed under standard theatre conditions on fresh cadaver eyes. This involved a corneal section, anterior capsulotomy, nucleus expression and lens matter aspiration with a hand held irrigation/aspiration coaxial cannula (0.3 mm port). Surgery was carried out under an

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operating microscope, and as complete a removal as possible was achieved, with Hartmann's solution for irrigation.

The eyes were then fixed in 10% formalin and washed in methyl alcohol. The specimens were cooled in isopentane and nitrogen to facilitate sectioning the globe in a coronal plane posterior to the lens capsule. The anterior segment was embedded in paraffin wax and stained with haematoxylin and eosin, and sectioned for histological examination.

TISSUE CULTURE

Normal lens epithelial tissue was obtained from human donor eyes used for corneal graft surgery within 36 hours of the death of the donor. The eye was bisected equatorially behind the ora serrata and the lens removed by cutting the suspensory ligaments. Cataractous lenses were obtained from patients at surgery by an intracapsular technique using forceps. The lens was then pinned, anterior surface down, to a Sylgard pad. After a circular incision had been made round the equator the posterior capsule, nucleus, and cortical lens matter were removed. The remaining anterior capsule with adherent epithelium was cut into rectangular strips such that each strip spanned the diameter of the lens capsule. Hence the central and equatorial cells were cultured.

The epithelial strips were laid flat on collagen coated Petri dishes and incubated in medium E199 + 50% fetal calf serum (FCS), penicillin/streptomycin (50 units/ml, 50 mg/l respectively) at 37°C (in a humidified atmosphere containing 5% CO₂). The serum concentration in the medium, originally 50%, was reduced to 36% on day 10, 25% on day 13, and 10% on day 16. Thereafter the medium (+ 10% FCS) was changed every three days.

CELL COUNTING

The outgrowth of cells was examined either by direct observation under phase contrast optics ($\times 4$, Nikon inverted microscope) or after fixation (ethanol:acetic acid), staining (Giemsa), and mounting (Aqualite).

Cellular outgrowth was determined by counting the number of cells along an axis perpendicular to the cut edge of the rectangular explant: (1) by means of photographic enlargements of fixed/stained cultures, or (2) directly on growing cultures under phase contrast optics.

To measure the outgrowth from specific regions of the explant after 35 days the fixed/stained cultures were examined under the microscope ($\times 26$); with a calibrated eyepiece graticule the extent of the outgrowth along three axes perpendicular to the explant edge was measured at the equatorial and central regions respectively, and these values were averaged. The results could be expressed in terms of length,

since variations in cell size were uniform within each culture, and each culture acted as its own control. This was not possible for comparisons of outgrowth between normal and cataractous lenses, since cell size increases with age of the culture. Thus, to avoid the possible inaccuracies that this size variation might introduce to measurements of outgrowth dimensions between cultures, it was decided to count individual cells along four axes perpendicular to the cut edge of the explant. Counts made on fixed/stained material, where much more detailed study was possible, acted as a check on the accuracy of the method, and all counts made by the method outlined above lay within one standard deviation of this more exhaustive method. Fig. 2 includes both sets of measurements.

AREA DETERMINATION

The area of cellular outgrowth was determined after 35 days of culture. The cultures were fixed, stained, and mounted as described above and placed over a grid (1 mm squares) and viewed under a dissecting microscope ($\times 20$). The total area (outgrowth plus explant) was determined by counting the number of squares covered and subtracting the area of the explant. The average cell diameter was determined by counting the number of cells along measured axes from the edge of the explant to the periphery of the outgrowth. With these two parameters it was possible to calculate the number of cells in the outgrowth. This value is an approximation and was not used as a criterion in experimental tests.

From the total number of cells produced before proliferation ceased and the number of parent cells (that is, the number of cells at the edge of the explant) the population doubling level (PDL) was calculated;

$$\text{PDL} = \log_{10} (N_t/N_0) / \log_{10} 2 \dots (1)$$

where N_t = total number of cells,
 N_0 = number of parent cells.

Results

After 35 days the cultures were fixed, stained, and mounted and the total area of cellular outgrowth was determined as described in 'Material and methods.' The average area of outgrowth for nine capsular/epithelial strips after 35 days in culture was 85.4 (SE 8.4) mm² (n=9). The cell diameter varied considerably from the edge of the explant to the periphery of the outgrowth, and this was a feature of all cultures. In a minority of cultures a limited degree of cell elongation was observed. Near the explant the cell diameter ranged from 30 to 50 μ m, while some cells in the outer regions had diameters in excess of 100 μ m. This compares with a diameter of 12 μ m for parent cells on the explant. From the area, πr^2 where $r=21.5$ μ m (calculated as described in 'Material and methods'), and the total area of cellular

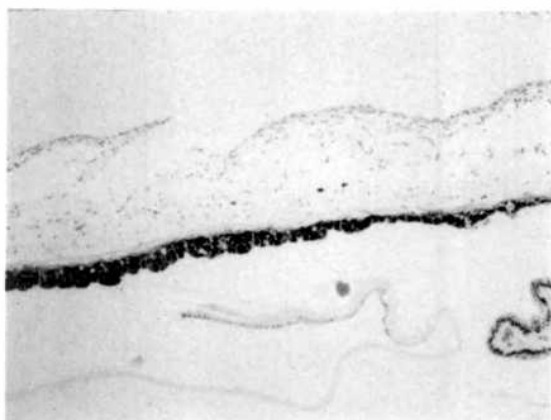


Fig. 1A

Fig. 1A Cross section of the human lens after simulated extracapsular lens extraction. While most of the soft lens matter is removed by irrigation, epithelial cells remain attached to the anterior and equatorial regions of the capsule.



Fig. 1B

Fig. 1B Enlargement of the equatorial region of the lens illustrating some residual cortical lens matter. The anterior and equatorial epithelial cells remain intact.

outgrowth it is possible to make an estimate of the number of new cells produced before the cessation of proliferation. For nine normal lens epithelial explants the average was 45 000. The population doubling level (PDL) can be calculated (equation 1) if the initial number of cells is known. The average area of the explants was 5.7 (SE 0.6) mm², which gives a value of 600–800 edge cells. On the assumption that these are the only cells available for proliferation, then from equation (1) the PDL achieved by these cultures of human lens epithelial cells was 6.

EXTRACAPSULAR CATARACT EXTRACTION IN VITRO

Histological study of the sections of the eyes showed that the remaining capsular bag was largely free of cortical lens matter (Fig. 1A), although small quantities were left in the equatorial regions (Fig. 1B). It was notable that in every case the epithelial cells remained intact and attached to the anterior and equatorial lens capsule. Normal irrigation/aspiration with Hartmann's solution did not remove these cells, which remained in their normal configuration on the anterior capsule remnants. There were no epithelial cells posterior to the equator.

CULTURED LENS CAPSULAR/EPITHELIAL STRIPS

After 3–5 days in culture cellular outgrowth from the explanted tissue was visible. This outgrowth continued as a monolayer for approximately 30 days and then stopped (Fig. 2), by which time the new cells extended about 5 mm from the edge of the explant.

In Fig. 2 the growth kinetics of explants from seven cataractous lenses and five normal lenses (six explants

from each lens) are compared. The data are presented as the average number of cells along an axis perpendicular to the cut edge of the explant (see 'Cell counting' under 'Material and methods'), as a function of time in culture. After a lag phase of about 2–3

CELL GROWTH FROM HUMAN LENS EPITHELIAL EXPLANTS

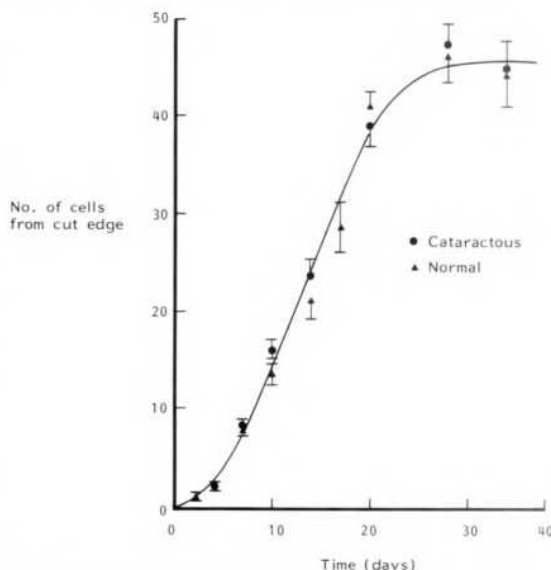


Fig. 2 Growth curves of epithelial cells from normal and cataractous lenses. The rate of outgrowth (y axis) is expressed as the number of cells from the cut edge of the capsular/epithelial strip. Each point represents the mean $\pm$ SE (bars) of explants from seven cataractous and five normal lenses. The plateau value of cellular proliferation represents six population doublings (see text).



Fig. 3A: Equatorial region of lens capsule.

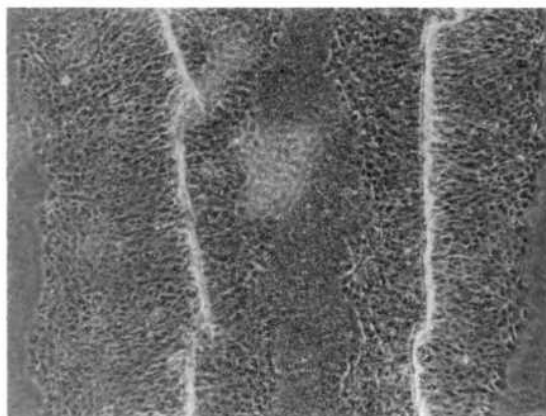


Fig. 3B: Central region of anterior lens capsule.

Fig. 3 Anteroposterior phase contrast micrographs of lens capsule strips after seven days in tissue culture. Daughter cells are growing both away from the cut edges on to the collagen substrate and also over the anterior surface of the capsule.

days the cells divided exponentially, reaching a plateau after about 28 days. No difference in growth characteristics was observed between explants from cataractous and normal lenses. At this stage no attempt was made to differentiate between types of cataract. Both cortical and nuclear as well as mixed cataractous types were used.

In neither normal nor cataractous explants was any difference in outgrowth between different regions along the strip of explant observed; central epithelial cells proliferated at the same rate as epithelial cells from the peripheral, germinative region (Fig. 3A and B), after 35 days the outgrowth extended 4.0 (SE 0.4) mm from the peripheral region and 4.4 (SE 0.3) mm from the central region ($n=9$).

The cells grew from the cut edge of the capsular/epithelial strip, not only on to the surface of the collagen substrate but also around and on to the anterior surface of the capsule (Fig. 3B).

Discussion

The cells of the central anterior lens capsule are considered to be arrested in the G_{0-1} phase of the cell cycle and hence not actively regenerating, while the cells at the equator retain their mitotic activity.⁴

The proliferation of these arrested cells in culture has been attributed to the tissue culture medium being richer in essential constituents than aqueous humour.⁵ However, ultrastructural studies of human posterior capsule membranes and Elschnig's pearls suggest that they are formed by proliferation of the epithelial cells without any change or enrichment of the aqueous humour.^{6,7} Other workers have suggested

that a retinal growth factor, uveal epithelial cells, and inflammation may play a role in stimulating anterior capsule cell proliferation.^{8,10}

Our culture model excludes the influence of all these possible factors and demonstrates that the primary site of cell proliferation is from the cut edge of the capsule. We believe that release from contact inhibition is a major factor in triggering cellular proliferation, since multilayering of cells is not observed in the initial stage. In our culture cellular proliferation was found to occur across any suitable surface: outwards across the culture substrate and around the anterior edge of the capsule. This has been noted in histopathological studies.¹¹ We found no significant difference in growth rate between cells from cataractous and normal lenses. We were limited in our choice of method for determining growth rate by the small amount of available starting material. Thus it was decided to opt for counting the number of cells from the edge of the explant as described in 'Material and methods.' Although this method may not be as precise (the error was estimated at 5%) as other cell counting techniques, such as ³H-thymidine incorporation or dye staining, these techniques necessitate the termination of culture and are less applicable to explant culture. Counting the number of cells eliminates errors due to variations in cell morphology that occur both with time and between cultures, and any measurement error due to the asymmetry of the outgrowth was reduced by counting cells from each of the sides of the rectangular explant and averaging the results. Contrary to our expectations based on animal studies,⁵ we found no difference in the growth potential between cells of the equator and those of the centre of the anterior capsule. Cytological studies have shown no dissimilarity between these cells.¹²

The finding that after six population doublings in

primary culture outgrowth ceases, and subsequently the outer epithelial cells become increasingly abnormal, is in agreement with the findings of Tassin *et al.*¹³ In the human, wrinkling of the posterior capsule may be caused by contraction of hyperplastic lens epithelial cells that have acquired myofibroblastic differentiation.¹¹ Retina derived growth factor has been shown to stimulate differentiation of rat lens epithelial cells, and it has been proposed that neural retina secretes a discrete factor(s) which interacts with epithelial cells as they are displaced into the vitreous compartment from the equator.^{9,14} In another study on mouse lens epithelial cells the formation of lentoid bodies could be triggered by the addition of a strip of capsule.¹⁵

The clinical implications of our study are that an anterior capsulotomy provides a stimulus for epithelial cell proliferation. Varying the location of the capsulotomy does not expose cells of greater proliferative potential. Creating a large capsulotomy will not reduce the risk of opacification by decreasing the number of epithelial cells in the eye, as suggested by Green and McDonnell.¹¹ On the contrary a large capsulotomy, especially if irregular or zig-zag as in the 'can opener' technique, releases a larger area of epithelial cells from contact inhibition. There is thus a theoretical advantage in performing a small capsulotomy or even a 'letter box' capsulotomy as in the endocapsular technique. Conversely the radial distance that proliferating anterior capsule cells have to migrate before occluding the visual axis is decreased with a small capsulotomy.⁷

In summary, our study has shown that after extracapsular cataract extraction the remaining anterior capsule has a normal pattern of epithelial cells that are firmly adherent to its posterior surface. The edge cells of the cut capsule can proliferate in culture. A significant factor governing their growth is loss of contact inhibition, and it is this loss of contact inhibition that is chiefly responsible for capsule opacification. The role of inflammatory mediators and growth and inhibitory factors in lens epithelial cell proliferation requires further study.

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Long-term results of treatment of idiopathic blepharospasm with botulinum toxin injections

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SUMMARY One hundred and one patients with idiopathic blepharospasm have been treated with injections of botulinum toxin A into the orbicularis oculi. Ten had previously had facial nerve avulsions and responded well, normal visual function being restored in the majority (7/10) for an average of 14 weeks. Without prior surgical treatment the response was more variable, but 71/91 regained normal or near normal vision. Older patients, those with a family history of the condition, and those without oromandibular dystonia responded slightly better. The severity of the blepharospasm, the length of the history, and spontaneous resolution of an episode of focal dystonia in the past had no influence on the outcome. Results were poor in the presence of an associated neurological disorder. Side effects, particularly a temporary partial ptosis, were common but were well tolerated. The average duration of improvement was eight weeks in men, nine in women, and there was no evidence of any increase in duration after multiple injections. Eighty nine patients continued with injections, 11 opted for surgical treatment, and one resumed drugs.

Botulinum toxin A is a dichain protein, with molecular weight 140 000, one of seven antigenically distinct neurotoxins produced by *Clostridium botulinum*, and a cause of the clinical syndrome of botulism, a progressive flaccid paralysis of muscle that follows ingestion of the toxin.¹ It can be purified and accurately quantitated, and, because of its specific binding to acceptors on motor nerve terminals, local injection of very small doses of the toxin produces local paralysis, and individual muscles can therefore be selectively weakened.² It interferes with the uptake of cytoplasmic acetylcholine by the presynaptic vesicles in the motor end-plate, and the duration and extent of the paralysis are dependent on the dose injected.^{3,4} Neuromuscular function is restored when new junctions are formed by sprouting from the axon, a process that takes six to eight weeks in the experimental animal.^{5,6}

A pharmacological treatment for strabismus was developed on this basis in the late 1970's⁷ and subsequently extended to idiopathic blepharospasm.^{7,8} At the dose used, no systemic immune response is encountered,⁹ and the treatment can be repeated indefinitely.

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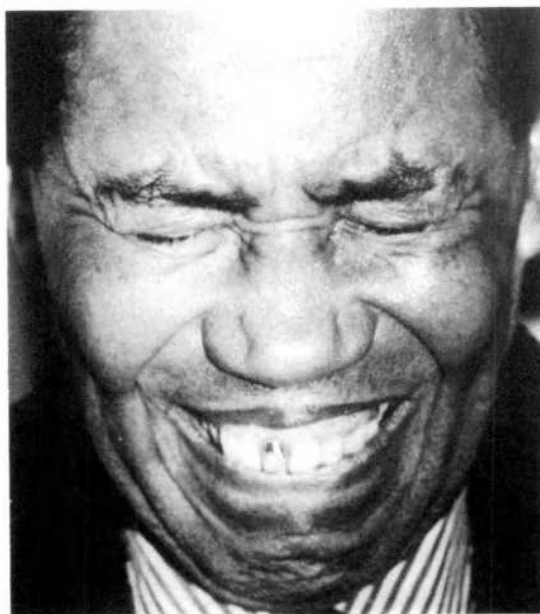


Fig. 1 Blepharospasm with oromandibular dystonia. The mouth is forced open and the jaw pulled down by spasm.



Fig. 2 Blepharospasm with facial grimacing. The patient associates the grimace with an effort to open the eyes.

Blepharospasm is characterised by repeated involuntary spasms of forceful lid closure, progressing to functional blindness, and may be associated with spasms of the muscles of the lower face and jaw (oromandibular dystonia, Fig. 1) or facial grimacing on attempted eye opening (Fig. 2). It usually begins insidiously in the 5th to 7th decade, and is probably due to organic dysfunction of the basal ganglia.¹⁰ Because of the disfiguring nature of the condition, and frequently diagnostic delays, anxiety and depression are often associated. Blepharospasm may also occur in extrapyramidal disorders such as Parkinsonism and progressive supranuclear palsy.

Drug treatment is usually ineffective, although benzhexol may be useful.¹¹ Denervation of the orbicularis oculi by facial nerve avulsion relieves the spasm, but the recurrence rate is 25% and upper facial mobility is abolished.¹² The combined orbicularis stripping and local denervation procedure may also be followed by recurrent spasm.¹³

The results in 101 cases treated with repeated injections of botulinum toxin, with a follow-up period of from 10 to 36 months, are presented in this report.

Patients, materials, and methods

Idiopathic blepharospasm was diagnosed clinically in 101 patients, 37 men and 64 women. The mean age at the onset of symptoms was 56.9 (range 26–74) and somewhat older in women (58.5) than men (55.3). Thirty-two had blepharospasm alone, 69 also had oromandibular dystonia, and, of these, 22 also had involuntary movements extending into the neck muscles which in eight interfered with eating or breathing. In 78 patients both with and without oromandibular dystonia attempts to open the eyes were associated with stereotyped facial grimacing and mouth opening. Five patients also had writer's cramp, three Parkinson's disease, two progressive supranuclear palsy, one tardive dyskinesia, and one generalised dystonia. There was a family history of focal dystonia in first-degree relatives in seven cases and in five an episode of focal dystonia had resolved spontaneously in the past (Table 1).

Most of the patients had been treated with a range of drugs without improvement, and 10 had had facial nerve avulsions, nine by one surgeon (22.5% of the total operations performed). In four cases the surgery had been repeated (in two twice), and a further three patients had had orbicularis stripping operations (one twice) and one stereotactic neurosurgery. The patient's visual disability was assessed on a functional scale, and graded from 1 to 6 (Table 2), and the same scale was used to assess the effects of treatment.

Botulinum toxin A in ampoules containing 0.05 µg freeze-dried neurotoxin was dissolved in 10 ml of sterile saline; the initial treatment was 1.6 ml of this

Table 1 Clinical features of patients treated

Total patients: 101	
Age at onset:	average 56.9 years (range 26–74)
Female 64	Male 37
Oromandibular dystonia	68.3%
Facial grimacing	78%
Neurological disease	7 patients (all male = 19% of men)
Parkinson's disease	3
Progressive supranuclear palsy (PSP)	2
Tardive dyskinesia	1
Generalised dystonia	1
Family history of focal dystonia	7
Other focal dystonia	9
Writer's cramp	5
Torticollis or retrocollis	4
Previous resolved episode of focal dystonia	4
Previous treatment drugs	93
Facial nerve avulsion	10
Orbicularis stripping	3
Stereotactic neurosurgery	1

Table 2 Scale used for assessment of visual function before and after treatment

Category	Visual function
1 Blind	Unable to see at all
2 Dependent	Needs assistance outside home environment
3 Independent	Poor function: can go out alone, cannot read or watch TV
4 Independent	Moderate function, can read a little, cannot work
5 Inconvenienced	Able to work, cannot drive a car
6 Normal	Full-time normal activity—working, driving

solution; 0.2 ml laterally and medially in the upper and lower lids. Half this dose was used in patients who had had facial nerve avulsion. The treatment was an outpatient procedure; patients were re-examined after two weeks and therefore at monthly intervals, or sooner if the spasm returned. Repeat injections are of between 50–75% of the initial dose, and all patients have received at least three separate sets of injections.

Results

After a latent period of 24 to 48 hours the intensity of the blepharospasm progressively lessened over 5 to 6 days. Seventy-eight patients were either completely relieved or only inconvenienced to a minor extent by residual spasms (Fig. 3). Of the remainder, four remained functionally blind or dependent due to a continuing Bell's phenomenon elevating the eyes behind open lids. Eight had only minimal

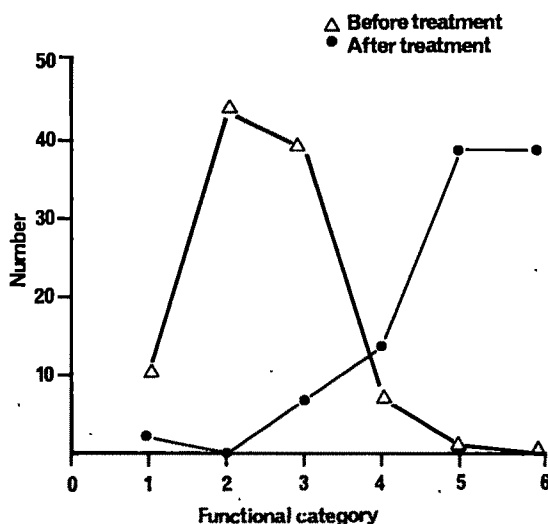


Fig. 3 Response to treatment in 101 patients with idiopathic blepharospasm.

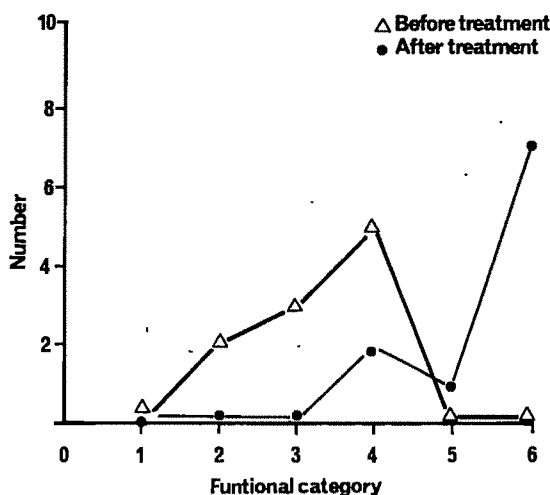


Fig. 4 Response to treatment in 10 patients who had previously had facial nerve avulsion.

improvement, while 11 were given some degree of independence. After a facial nerve avulsion there was generally a good result (Fig. 4), but orbicularis stripping had no influence on the response. Of the remainder, older patients had a marginally better response, as did those with no oromandibular dystonia or with a family history of focal dystonia. The length of the history or spontaneous resolution of an episode of dystonia in the past had no influence. In the presence of generalised neurological disease the results were poor.

Symptomatic improvement or relief lasted on average nine weeks, appreciably longer after a facial nerve avulsion (14 weeks); women had a slightly better sustained response than men (nine weeks compared with eight), but no other variable feature, such as age, severity, or length of history had any influence.

Sixteen of the 69 patients with oromandibular dystonia found that their facial movements were reduced or abolished when the blepharospasm was relieved, while facial grimacing associated with the effort to open the eyes was always relieved when the upper face spasm was reduced.

The commonest side effect was lid swelling, occurring in most cases after each treatment and resolving in one to two weeks. A more severe ptosis with reduced levator function was also common, occurring every third or fourth injection in half the patients, but it was short lived and did not affect visual function (Table 3). Three cases of profound ptosis with extraocular muscle weakness due to inadvertent overdosage took up to seven weeks to recover fully, and in six other patients there were episodes of temporary diplopia due to either inferior

Table 3 *Temporary side effects*

Side effect	Number	Period to resolution (weeks)
Periorbital tissues		
fluid accumulation	92	2-3
Ptosis with reduced levator function	50 after 4 injections	2-3
Mild		
Severe	3	7
Diplopia		
Superior rectus underaction	2	3
Inferior oblique underaction	4	3

Table 4 *Follow-up: long-term treatment*

Treatment	No of patients
Repeated injections with maintenance of improvement	89
Resumption of systemic drug treatment	1
Surgical treatment	
Facial nerve avulsion	8
Orbicularis stripping	3
Resumption of injections after surgery	4

oblique or superior rectus underaction. Although the dose of toxin needed to sustain the improvement diminished with repeated injections, the interval between treatments remained the same.

Eighty nine patients have continued with injection treatment, one has resumed drugs, and 11, after between three and five sets of injections, have had surgical treatment (Table 4). Four have subsequently had to resume injections owing to a recurrence. This group all had oromandibular dystonia and a poor or ill-sustained response to botulinum toxin but were neither more severely affected nor more subject to side effects.

Discussion

The clinical features of patients treated in this study were typical of idiopathic blepharospasm,¹⁰ with onset in the 6th decade, a high incidence of oromandibular dystonia, and a female preponderance. Drug treatment had either not been successful or produced too many side effects. Within two weeks of the first injection 77% were substantially improved, with 39% functioning normally. Although the duration of symptomatic relief was only nine weeks, there was detectable weakness of the orbicularis oculi for much longer, and the muscle probably has to be reduced to less than 90% of its normal strength to allow the eyes to stay open.¹⁴ The dose needed to sustain this degree of weakness of the orbicularis declines with successive injections, but there is no increase in the



Fig. 5 *Persistent Bell's phenomenon after treatment. Despite profound weakness of the orbicularis oculi, the patient remains functionally blind, as the eyes move up under the upper lids.*

period of relief, and sprouting from the terminal axon must be continuing. After a facial nerve avulsion recovery of muscle power takes substantially longer, and, since the treatment makes the orbicularis no weaker than in unoperated cases, the regenerated axon must be less capable of sprouting.

Bell's phenomenon is a normal accompaniment of forceful lid closure, and presumably present in all patients before treatment. Four patients remained visually disabled by it after treatment (Fig. 5), so that in the remainder paralysing the orbicularis must have abolished the associated eye movement. In the same way oromandibular dystonia was indirectly relieved or improved in a substantial minority. The explanation is not clear. Motor activity elsewhere in the body – for example walking – often exacerbates blepharospasm and oromandibular dystonia, presumably by a central mechanism. Relief of one aspect of abnormal motor function by peripheral paralysis must influence related movements centrally. Facial grimacing, although sometimes described by the patient as a voluntary attempt to open the eyes, has dystonic features, being a stereotyped movement, often associated with torsional neck movements, and it is also always abolished if the eyes can be opened.

The poor response in the presence of Parkinson's disease and progressive supranuclear palsy (PSP) may indicate differences in the pathophysiology of the difficulty in opening the eyes, particularly in PSP. The lids are not usually forcefully squeezed but rather cannot be voluntarily opened, and reflex blinking is normal, suggesting an apraxia of eyelid opening that is not influenced by weakening the orbicularis.

Side effects of the treatment are common. Tissue fluid accumulation in the lids is almost invariable, and because of prolonged spasm many patients also have a brow ptosis and stretching or disinsertion of the upper lid levator. In four cases brow fixation or levator advancement has been a helpful adjunct to injection treatment. A mild (1-2 mm) asymmetric ptosis, due to spread to the levator, occurred in half the patients on one occasion after four or more injections, but was short lived and well tolerated. An episode of diplopia developing three or four days after the injection and due to spread of paralytic effect to the superior rectus (three cases) or inferior oblique (four cases) resolved within a maximum of three weeks, with the symptoms being controlled by prisms. A complete ptosis with external ophthalmoplegia occurred in three cases after an inadvertent 10-fold overdose of toxin. All these cases recovered normal lid opening and ocular muscle function, but the eldest patient took up to seven weeks to do so. The blepharospasm returned after a further eight to 10 weeks, and all these patients have had at least two further sets of injections without incident.

The 11 patients who elected to have surgical treatment (Table 4) obtained little or very short lived relief from injections. They did not have an excess of side effects and were not distinguishable before treatment from those who responded well. In four cases with persistent Bell's phenomenon the problem remained after successful facial nerve avulsion, but it resolved after six weeks in two patients. Four of the 11 patients treated surgically (three facial nerve avulsions, one orbicularis stripping) have had to resume injections, and in the patient who had had muscle surgery subcutaneous scarring made this very uncomfortable.

Conclusion

Botulinum toxin treatment is a safe and effective way of controlling idiopathic blepharospasm, and at the same time in the majority of cases relieving facial grimacing. Associated dystonic movements may also be indirectly improved in a minority.

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Recurrent herpes simplex virus ocular infection: epidemiological and clinical features

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SUMMARY The epidemiological and clinical features of recurrent herpes simplex virus ocular infection (RHSV) were studied. Of 108 patients with primary herpes simplex virus ocular infection (PHSV) who were followed up for two to 15 years 35 (32%) suffered one or more recurrent attacks. The recurrence rate was significantly higher in patients under 20 years of age, but there was no significant difference between recurrence rates in males and females. Of 35 patients with RHSV 17 (49%) had one recurrent attack, 14 (40%) had between two and five, and four (11%) had between six and 15 attacks. The mean time interval between PHSV and the first four RHSV attacks was 10 months, and was shorter in subsequent attacks. The duration and severity of RHSV were reduced in successive recurrences. Patients with more severe conjunctivitis and lid lesions during PHSV ocular infection had a higher incidence of recurrent infection. The severity of the corneal signs in PHSV had no influence on the incidence of recurrent infection. Several clinical forms of RHSV were observed. Conjunctivitis associated with lid lesions was observed in 29 (83%) patients. In six (17%) patients the disease presented as an acute follicular conjunctivitis without characteristic lid or corneal lesions. Dendritic ulcer was found in three (9%) patients, and in one of them it was associated with a disciform keratitis. A chronic blepharoconjunctivitis developed in eight (23%) patients. The epidemiological and clinical features of RHSV were compared with those of PHSV.

In a previous report¹ we presented the epidemiological and clinical features of primary herpes simplex virus (PHSV) ocular infection in patients attending an ophthalmic clinic in London. We found that primary ocular infections were commoner in the age group 15-20 years than in others and that in one-third of the patients it was associated with systemic disorder. The commonest clinical form observed was conjunctivitis with associated lid lesions. Follicular conjunctivitis without lid or corneal lesions, dendritic ulcer, and disciform keratitis were also found.

In this report we present epidemiological and clinical features of recurrent herpes simplex virus (RHSV) ocular infection in patients who were included in our study of PHSV ocular infection.¹

Patients and methods

One hundred and eight patients with PHSV attending

the External Eye Diseases Clinic at Moorfields Eye Hospital were followed up for recurrent attacks for two to 15 years. The criteria for the diagnosis of PHSV and the epidemiological and clinical features are presented elsewhere.¹

The methods of clinical examination and virus isolation in patients with RHSV were carried out as described previously.^{2,4} A diagnosis of RHSV ocular infection was based on the detection of herpetic lid vesicles and/or ulcer, corneal ulcer, or HSV isolation from the conjunctiva. Statistical analysis was carried out by χ^2 tests.

Results

Age and sex. Of 108 patients with PHSV ocular infection 35 (32%) developed one or more attacks of RHSV ocular infection. Their ages ranged from 18 months to 56 years, mean 18 years. The distribution of patients' ages in relation to PHSV and RHSV ocular infections is shown in Fig. 1. The prevalence of RHSV ocular infection in patients under 20 years of

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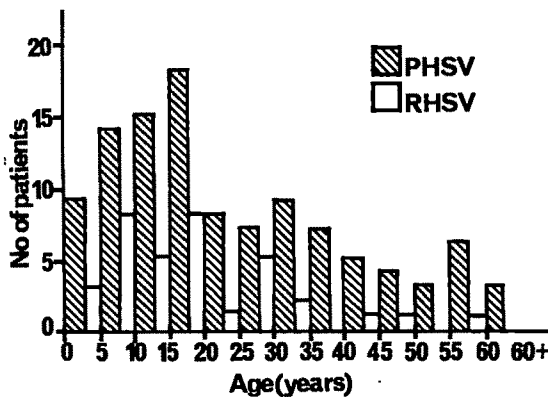


Fig. 1 Age distribution of 108 cases of PHSV and the 35 patients who developed RHSV ocular infections.

age was significantly higher than that observed in the older patients ($p < 0.03$, Table 1). RHSV developed in 16 of 58 (28%) male patients and in 19 of 50 (38%) female patients with PHSV. This difference is not statistically significant ($p > 0.05$).

Seasonal variation. The seasonal variation of prevalence of PHSV and RHSV was similar, being

Table 1 Association between epidemiological and clinical features of PHSV and incidence of RHSV

PHSV		Incidence of RHSV		P Value
Features	No.	No.	%	
Age:	under 20	56	24 (43%)	$p < 0.03$
	over 20	52	11 (21%)	
Sex:	female	50	19 (38%)	
	male	58	16 (28%)	
Laterality:	bilateral	20	9 (45%)	
	unilateral	88	26 (30%)	
Atopicity:	atopic	16	7 (44%)	
	non-atopic	92	28 (30%)	
With non-ocular HSV		18	4 (22%)	
Without non-ocular HSV		90	31 (34%)	
Associated URTI		23	11 (48%)	
Without associated URTI		85	24 (28%)	
Lid lesions:	nil	8	1 (12%)	$p < 0.01$
	mild	58	13 (22%)	
	moderate	31	15 (48%)	
	severe	11	6 (55%)	
Conjunctivitis:	mild	50	6 (12%)	$p < 0.001$
	moderate	41	18 (44%)	
	severe	17	11 (65%)	
Keratitis:	nil	72	22 (31%)	
	punctate keratitis	36	13 (36%)	
	dendritic ulcer	16	4 (25%)	
	disciform keratitis	2	1 (50%)	

URT I = upper respiratory tract infection.

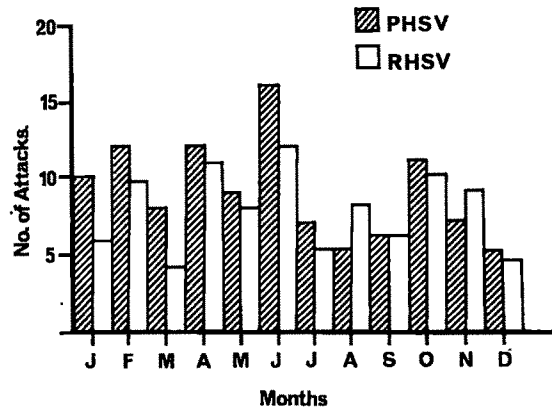


Fig. 2 Seasonal variation of 108 cases of PHSV ocular infection and the 93 subsequent attacks of RHSV ocular infections in 35 patients.

highest in June, but without any clear seasonal pattern during the rest of the year (Fig. 2).

Number of recurrences. Of 35 patients with RHSV ocular infection 17 (49%) had one recurrent attack, 14 (40%) two to five, and four (11%) six to 15 attacks. The total number of recurrences was 93. In females RHSV attacks were evenly distributed in relation to age, but in males they were commoner in those under 15 years of age (Table 2).

Interval between attacks. The time interval between PHSV and the first RHSV ocular infection ranged from one month to four years, mean 10 months. The intervals between second, third, and fourth attacks were very similar, but in patients with more than four attacks the intervals were generally shorter, ranging from one to five months.

Duration and severity of attacks. The duration of each attack was usually shorter than the preceding one. PHSV ocular infection lasted 2.8 weeks on average, whereas the first recurrence lasted 1.8 weeks, the second 1.7 weeks, the third to sixth 1.4 weeks, and subsequent recurrences lasted for one week. The severity of disease was similarly reduced with successive recurrences.

PHSV severity and recurrence rate. Patients with more severe conjunctival signs during PHSV ocular infection had a higher incidence of recurrent infection than patients with less severe conjunctival signs (Table 1). This difference was statistically significant

Table 2 Number of recurrences in relation to sex and age

	Females Patients/recurrences	Males Patients/recurrences
Under 15	9/23	7/26
15 and over	10/28	9/16

Table 3 Prevalence of symptoms in 35 patients during their first recurrent attack

Symptoms	Number of patients	%
Redness	21	60
Lid vesicles	17	49
Irritation and itching	16	46
Swelling of lids	15	43
Discharge	14	40
Watering	9	26
Photophobia	7	20
Blurred vision	6	17
Pain	4	11

($p < 0.001$). The severity of lid lesions was similarly related to a higher incidence of RHSV ($p < 0.01$). The recurrence rate also tended to be higher in patients with bilateral PHSV or with an associated upper respiratory tract infection, but it was not statistically significant ($p > 0.05$). The severity of the corneal signs had no influence on the incidence of recurrent infection in contrast to lid and conjunctival signs.

Symptoms. The common symptoms during recurrences were mild to moderate redness, itching, irritation, lid swelling, and lid vesicles and/or ulcers. The frequency of symptoms during the first recurrent attack is shown in Table 3.

Signs. The major signs were associated with the lid, conjunctiva and cornea (Table 4).

Vesicles and/or ulcers of the eyelids occurred in 29 (83%) patients. These were moderate in four (11%) and mild in 25 (71%). Six (17%) patients had no lid lesions during the first RHSV ocular attack, but three of these developed lid lesions during second or subsequent recurrences. In eight (23%) patients a chronic blepharitis consisting of mild to moderate lid margin erythema, swelling, scales, and meibomianitis developed in association with conjunctivitis. Only two of these eight patients had developed chronic blepharitis after their PHSV ocular infection.

The bulbar conjunctiva showed mild or moderate hyperaemia in 17 (49%) and four (11%) patients respectively. In the palpebral conjunctiva a papillary reaction was severe in one patient (3%), moderate in 12 (34%), and mild in 22 (63%). In 14 (40%) patients small and discrete follicles were found mainly in the lower lid conjunctiva.

Corneal signs were found during first or subsequent recurrences in 10 (24%) patients. They included fine punctate keratitis in seven patients and dendritic ulcer in three. In one patient dendritic ulcer occurred during the first recurrence and in two patients during the second recurrence. In one patient dendritic ulcer was associated with disciform keratitis. In PHSV 16 (15%) patients had dendritic ulcers.¹ Only five of

Table 4 Severity of signs during first recurrent attack

Area	Signs	Absent	Mild	Moderate	Severe
Lids	Vesicles and/or ulcers	6	25	4	0
Bulbar conjunctiva	Hyperaemia	14	17	4	0
Palpebral conjunctiva	Papillae	0	22	12	1
	Follicles	21	0	14	0
Cornea	Epithelial punctate keratitis	28	0	7	0
	Dendritic ulcer	34	1	0	0
	Disciform keratitis	34	0	1	0

these 16 (31%) developed a recurrent infection. Three of these who developed recurrences had normal corneas, one had only fine punctate epithelial keratitis, and one developed dendritic ulcer.

Virus isolation. Conjunctival specimens were collected from only 10 patients with RHSV, and virus was isolated from four of these.

Discussion

The results of the present study show several important epidemiological and clinical features of RHSV. The RHSV rate of 32% in our series is comparable with the rate of 40% reported earlier.³ In our patients the incidence of RHSV was significantly higher in males than in females and in males aged under 15. In the earlier studies it was found that RHSV was commoner in males aged 25 years and over than in males under 25 and in females.^{3,4} The cause of this increased susceptibility of males to recurrences is not known.

It is interesting to note that in our series the RHSV rate was closely associated with the overall severity of the PHSV, and in particular with the severity of the lids and conjunctival lesions. In contrast, however, there was no association between the severity of corneal disease and prevalence of RHSV. We have found that there are larger numbers of infectious virus particles in infected skin and conjunctiva compared with the cornea (unpublished observations). Hence it is possible that, when larger numbers of HSV particles are present, infection of the sensory ganglion may be facilitated, leading to a higher rate of recurrence.

The clinical presentation of RHSV in our group of patients is different from that in previous reports. It has generally been accepted that RHSV occurs mainly in the form of ulcerative keratitis, though occasionally it may present as conjunctivitis with or without lid lesions.^{8,10} In our series of patients with RHSV we found that corneal ulcers developed in only three of 35 (9%) patients. In the remaining

patients the disease presented as conjunctivitis with or without lid lesions and was slightly milder than the preceding episode. These findings indicate that corneal ulcer and stromal keratitis may occur in only a small proportion of patients with RHSV. In comparison, dendritic ulcer was detected in 16 (15%) patients during PHSV.¹ Only five of these 16 (31%) developed recurrent disease, and only two of these had corneal involvement during recurrent disease. These observations indicate that corneal involvement in PHSV does not necessarily carry a poor prognosis.

A chronic blepharitis was detected in eight (23%) patients with RHSV. Of these, only two had similar problems during PHSV.¹ The development of a chronic blepharitis in association with PHSV or RHSV suggests that HSV is either the cause of chronic blepharitis or is a predisposing factor for the development of a secondary bacterial blepharitis.

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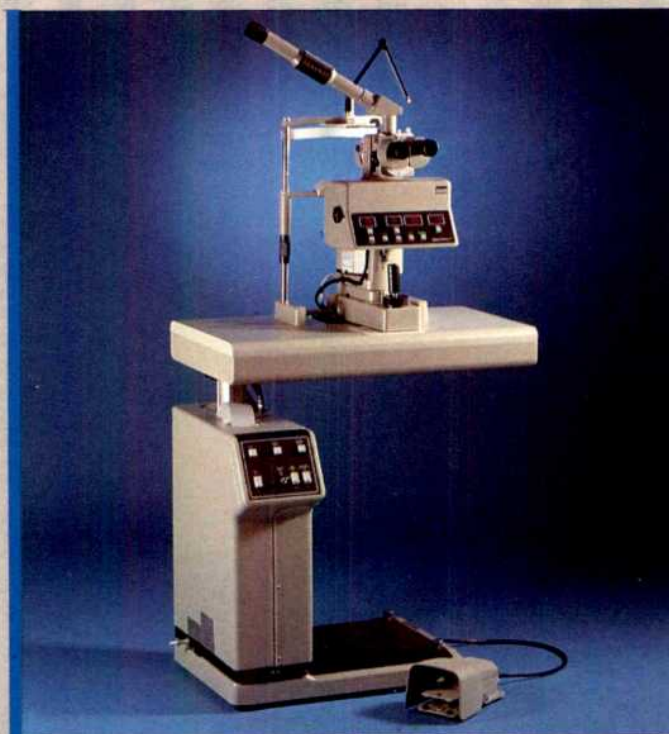
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Value and cost effectiveness of double culture tests for diagnosis of ocular viral and chlamydial infections

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SUMMARY Swabbings from the eyes of 4132 patients attending ophthalmic casualty and out-patients clinics were tested for chlamydiae, adenovirus, and herpes simplex virus. Laboratory isolation tests gave positive results for one of these three agents in 696 (16.8%) cases. When a positive isolation was obtained, only 341 (49%) agreed with the clinical diagnosis while 355 (51%) either had no definite diagnosis marked on the request card or had been clinically diagnosed incorrectly. Routine testing of ocular specimens for all likely organisms can enable the correct treatment to be started sooner than doing one test at each visit, thereby reducing the number of times the patient has to visit the clinic and the expenses involved.

Adenovirus, herpes simplex virus (HSV), and *Chlamydia trachomatis* are common causes of conjunctivitis and keratoconjunctivitis.¹ The clinical differential diagnosis of these ocular infections is difficult, particularly in the early stages of infections or in the absence of typical signs.² In a recent study of acute conjunctivitis in an outpatient ophthalmic clinic in London it was found that in only 16% of cases was the clinical diagnosis correct as confirmed by laboratory tests. In this paper we present the results of double culture tests for *C. trachomatis*, HSV, and adenovirus in 4132 unselected consecutive patients who attended the clinic because of conjunctivitis or keratoconjunctivitis. The value and cost effectiveness of the double tests in the diagnosis and management of these ocular infections are discussed.

Materials and methods

All specimens received in the laboratory during a period of 15 months from unselected consecutive cases of conjunctivitis or keratoconjunctivitis were included in this study. Conjunctival specimens were collected by swabbing and stored in 2SP transport medium³ at -70°C until inoculated. Each specimen

was divided into two aliquots, one for culture for *C. trachomatis* and the other for adenovirus and HSV.

Cultures for *C. trachomatis* were performed with cycloheximide treated McCoy cells⁴ or McCoy cells pretreated with mitomycin-C (unpublished method):

For viral isolation the rapid culture test for adenovirus⁵ and herpes simplex virus was used.⁶

Results

The results from the 4132 specimens tested and their respective clinical diagnoses are shown in Table 1. The total number of positive cultures was 696 (17%); 341 of these positives were in tests specifically

Table 1 Isolation results compared with clinical diagnosis

Clinical diagnosis	Total	Laboratory diagnosis		
		Chlamydia No. (%)	Adenovirus No. (%)	Herpes No. (%)
Chlamydial	804	88 (10.9)	51 (6.3)	7 (0.9)
Adenovirus	909	21 (2.3)	217 (23.9)	14 (1.5)
Herpes simplex	264	1 (0.4)	3 (1.1)	36 (13.6)
Herpes zoster	2	0	0	0
Bacterial	45	1 (2.2)	1 (2.2)	0
Allergic	41	1 (2.4)	1 (2.4)	0
Multiple or no aetiological diagnosis*	2067	45 (2.2)	172 (8.3)	37 (1.8)
Total	4132	157 (3.8)	445 (10.8)	94 (2.3)

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*This includes patients for which no diagnosis was given on the card and also those cards which indicated uncertainty between two or more possible diagnoses.

Table 2 Comparison of laboratory diagnosis with provisional clinical diagnosis

Laboratory diagnosis	Number positive	Concordant clinical diagnosis (%)	Discordant clinical diagnosis (%)	Multiple or no aetiological diagnosis (%)
Chlamydia	157	88 (56.1)	24 (15.3)	45 (28.6)
Adenovirus	445	217 (48.8)	56 (12.6)	172 (38.7)
Herpes simplex	94	36 (38.3)	21 (22.3)	37 (39.4)
Total	696	341 (48.9)	101 (14.5)	254 (36.5)

requested by the clinician. The double culture tests increased the number of positives by 355 (104%).

A clinical diagnosis was indicated on the request card in only 2065 cases. *C. trachomatis*, adenovirus, or HSV was isolated from 442 (22.4%) of these. Only 341 (77.2%) of these isolations agreed with the clinical diagnosis while in 101 (22.8%) cases the clinical diagnosis was shown to have been wrong (Table 2).

In 2067 cases no precise aetiological diagnosis was marked on the request card. Positive isolations were made in 254 (12.3%) of these (Table 1).

Discussion

The inadequacy of relying on clinical diagnosis for ocular infections has been pointed out previously.² The results presented here are generally in accord with those obtained by Wishart and colleagues² and emphasise the difficulty in distinguishing between chlamydial, viral, bacterial, and allergic conjunctivitis solely on clinical grounds (Table 1). Of those specimens which gave a positive isolation result 51% had either been diagnosed incorrectly or had no definite clinical diagnosis (Table 2).

The clinical diagnosis which appears to have been most certain was that of HSV infection with lid or corneal lesions, as only four (1.5%) cases which were clinically diagnosed as HSV were shown to be due to chlamydia or adenovirus. This is presumably because of the presence of typical signs of HSV in the cornea and/or lids. However, 58/94 (61.7%) of HSV isolations were obtained from cases which were not recognised by the clinicians; 21 (22.3%) being diagnosed as either chlamydia or adenovirus and 37 (39.4%) diagnosed only as conjunctivitis. This is probably because HSV was not considered as a possible cause in the absence of typical lid or corneal lesions. Previous reports have shown that HSV can cause acute conjunctivitis without these 'typical' clinical signs.⁷

There appeared to be rather more confusion between chlamydial and adenoviral infections. Twenty-one of 157 (13%) chlamydial isolations had

been clinically diagnosed as adenovirus and 51/445 (11%) of adenovirus isolations had been diagnosed as due to chlamydia. The confusion over the clinical diagnosis between chlamydial and adenovirus infections is due to the similarity of their clinical signs during the early stages of infection.²

In this study only 49% of the cases with positive isolations were correctly identified by the clinician, and the remaining 51% would have been missed unless the patients had further visits and tests so that a definite diagnosis could be made and the correct treatment given. Traditionally, a diagnostic laboratory performs only those tests requested by the clinician, who is encouraged to minimise costs by asking for a single test to confirm his diagnosis. Any specimens which arrive without some indication of the tests required must either be discarded or delayed while the clinician's intention is ascertained. In this series approximately half of the specimens tested did not have an accompanying clinical diagnosis, but it seems likely that if the clinician had been pressed to give one it would not have been any more accurate than those diagnoses given voluntarily.

This study included only specimens which had been sent to the laboratory for either chlamydial or viral diagnosis, so the number of specimens from conditions clinically diagnosed as bacterial or allergic is small. However, the results suggest that at least 5% of these may in fact be chlamydial or viral.

It may be argued that the expense of carrying out double tests on specimens from all patients is prohibitive. In an established laboratory we estimate that the cost in material and technician time of performing an extra culture test is about £3.00. The extra cost of performing double tests compared with single tests on 4132 specimens was therefore about £12 396. Against this must be set the savings and benefits of more rapid diagnosis and management of the infections. It has been estimated that the direct and indirect costs of a visit to an outpatient clinic under the National Health Service is £70, and that the provision of adequate laboratory tests on the first visit of the patient to the clinic leads to an average saving of three follow-up visits to the clinic which would otherwise be needed before a definite diagnosis is made.² In this study the testing of all specimens for both *C. trachomatis* and viruses led to the diagnosis of 355 extra cases, an improvement of 104%. On this basis the average saving by provision of adequate laboratory tests for these extra positions amounted to £74 550 (£210 per patient). The net saving of performing the double culture tests was therefore about £62 154. To this we should add the benefits to the patients of better management by providing a positive or negative diagnosis for chlamydia, adenovirus, or HSV as the cause of an

infection, and savings by reducing the number of outpatient visits and allowing the patients with negative tests to be discharged earlier than would otherwise be the case.

The testing of specimens for the three major causes of conjunctivitis during the first visit to the clinic is therefore a practical and comparatively inexpensive procedure which is of benefit both to the patient through the earlier start of the correct management including treatment and preventive measures, and to the health units by reducing the load on the clinic and limiting the number of follow-up visits required.

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‘Blow-outs’ in the retinal pigment epithelium

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SUMMARY A hole was detected in the epithelium of a retinal pigment epithelium (RPE) detachment in two patients. Leakage through the hole led to an elevation of the overlying neurosensory retina in each case. The resulting vision was 20/70 in one eye and 20/30 in the other. The defects in the RPE occurred in a setting different from that usually seen with tears in the pigment epithelium and had a different clinical appearance.

Two patients were seen who had a defect in the epithelium of a retinal pigment epithelium (RPE) detachment underlying a neurosensory retinal elevation. These defects were confirmed by stereobiomicroscopy and stereophotography. They were not similar to the RPE tears or holes which have been previously described.^{1–4} Fluorescein angiography demonstrated intense leakage through the defects in each case. In one patient the evolution of the defect suggested that build-up of fluid pressure in the RPE detachment led to a ‘blow-out’, causing the defect and subsequent intense leakage with its overlying neurosensory detachment. We believe our patients had a variant of central serous choroidopathy, and the observations made here on the aetiology of the

RPE defects may be applicable to all cases of this disease.

Case reports

CASE 1

In November 1984 a 50-year-old man was examined who had noted a gradual decrease in vision of his left eye over the preceding three months. He had had a cardiac transplant 15 months earlier and was taking cyclosporin, prednisone, frusemide and hydralazine. The best visual acuity was 20/30 in the right eye and 20/70 in the left eye with a mild hyperopic shift in comparison with his current correction. The Amsler grid testing and fundus examination in the right eye were normal. In the left eye there was a 1½ disc diameter neurosensory detachment centred infero-temporal to fixation (Fig. 1). The edge of the

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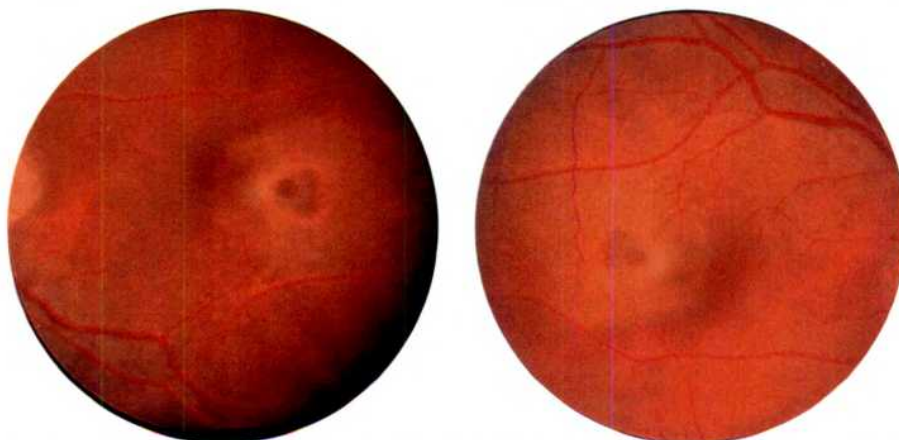


Fig. 1 Case 1. Left eye stereopair: 1½ disc diameters of subretinal fluid with RPE defect at the dome of an RPE detachment (white dot is artefact).

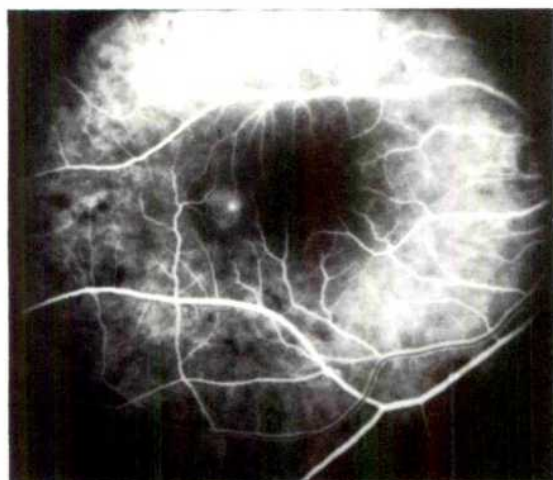


Fig. 2

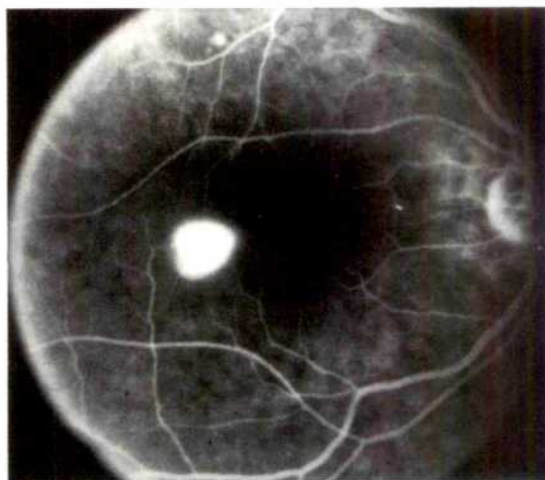


Fig. 3

Figs. 2, 3 Case 1. Fluorescein angiograms reveal early pinpoint hyperfluorescence in the area of the RPE defect, with progressive fluorescence through the defect into the subretinal space in the later frame. Note transmission defects temporally.

subretinal fluid just reached the centre of the macula. Underlying the central one-third of the subretinal fluid was an RPE detachment with a 400 μ m defect in the RPE at its apex.

Fluorescein angiography revealed early even filling of the RPE detachment (Fig. 2). At the apex of the detachment a hot spot was seen which correlated with the RPE defect seen clinically (Fig. 3). The defect leaked dye early and progressively into the subretinal

space. In late views the definition of the RPE detachment was lost owing to the accumulation of dye in the overlying subretinal space. Late phase photographs in the right eye were normal. The patient died soon after the examination.

CASE 2

On 10 November 1983 a 31-year-old man presented with a two-day history of metamorphopsia in the

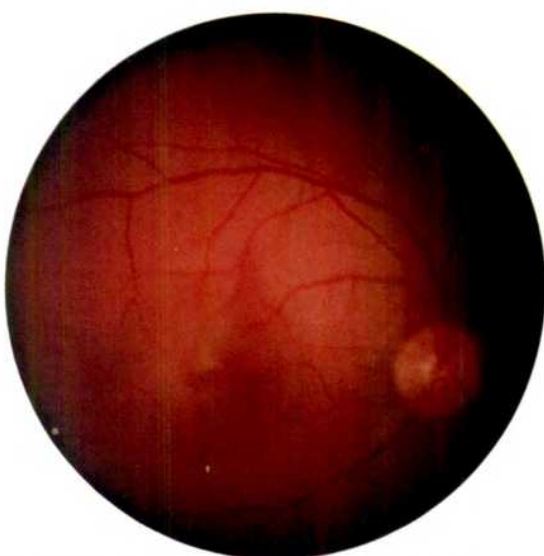


Fig. 4 Case 2. Right eye, 10 November 1983. One disc diameter subretinal fluid with greyish elevation of RPE just temporal to fixation.

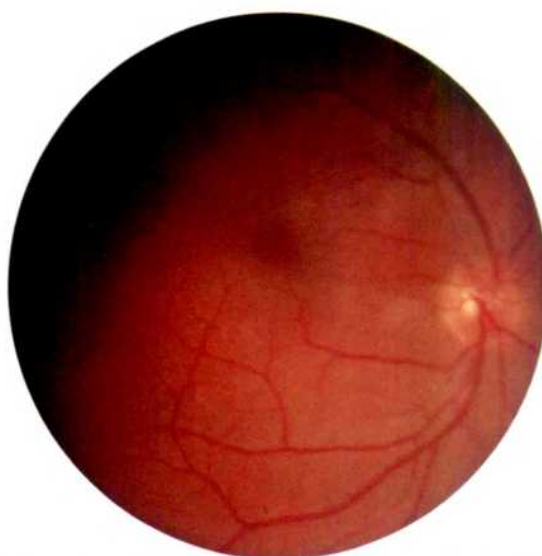


Fig. 5 Case 2. Left eye, 10 November 1983. Scattered subtle areas of pigment rarefaction and small area of subretinal fluid temporal to the disc.

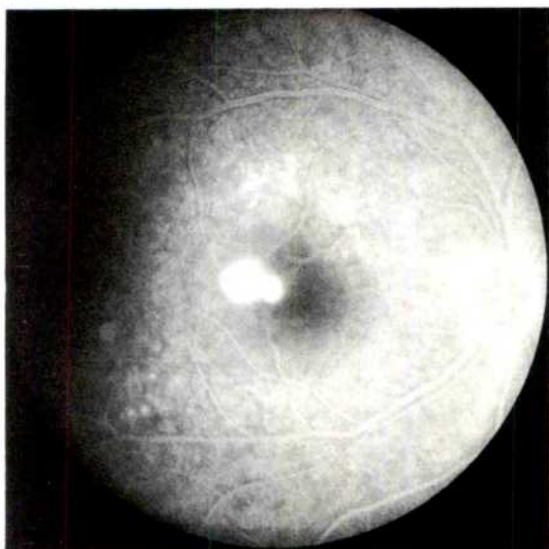


Fig. 6

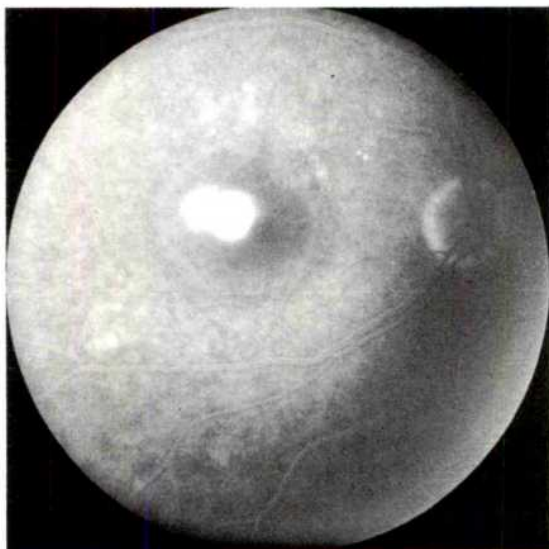


Fig. 7

Figs. 6, 7 Case 2. Right eye, 10 November 1983. Fluorescein angiogram reveals bilobed hyperfluorescence with early more intense leak from the nasal lobe, which increases dramatically as the angiogram progresses (temporal lobe of fluorescence is probably a small RPE detachment).

right eye. He had had an aortic resection four years previously for a traumatic aneurysm and was on propranolol and triamterene plus hydrochlorothiazide (Dyazide) for hypertension.

The best acuity was 1/200 in the right eye and 20/20 in the left eye with a mild hyperopic refraction. Retinoscopy revealed a 2 dioptre increase in hyperopia in comparison with his spectacle correction in the right eye. On Amsler grid testing in the right eye there was a large central 'grey spot'. The left eye had a normal grid pattern. An afferent pupillary defect was present in the right eye. In the right eye there was a neurosensory detachment 1500 μ m in diameter overlying a whitish grey elevation of the RPE which was 500 μ m in diameter and located just temporal to the centre of the macula (Fig. 4). No blood or exudate was seen. In the left eye there was an area of subretinal fluid just temporal to the disc about 750 μ m in diameter, multiple areas of pigment rarefaction, and a large druse just inferonasal to the fovea (Fig. 5).

Fluorescein angiography in the right eye revealed a bilobed area of leakage through the RPE just temporal to fixation, with the more nasal aspect increasing dramatically in size, as the angiogram progressed and the dye accumulated in the subretinal space (Figs. 6, 7). In the left eye there were multiple transmission defects in the posterior pole, some of which correlated with areas of pigment rarefaction seen clinically, and a slow pooling of dye in the

neurosensory detachment just temporal to the disc (Fig. 8).

On 14 November 1983 the subretinal fluid in the right eye had increased to involve the entire area within the arcades (Fig. 9). On 22 November the subretinal fluid in the right eye was the same, but in the left eye it had extended into the centre of the macula, causing the vision to decrease to 20/50. On 4 January 1984 the neurosensory elevation in the right eye had decreased dramatically, so it was only approximately 1½ disc diameters in extent. However, a yellowish opalescence of the retinal pigment epithelium had now appeared beneath it (Fig. 10). Within this opalescent RPE there was an RPE defect at the spot where a whitish grey RPE elevation had been noted on 10 November. Fluorescein angiography in the right eye continued to show a bilobed leak in the RPE just temporal to fixation, though the 'temporal lobe' was much less prominent than on 10 November 1983. The nasal lobe continued to leak intensely and correlated with the RPE defect. A small RPE detachment was seen clinically and on fluorescein angiography inferonasal to the fovea in the left eye in an area previously noted to have a transmission defect.

On 28 February 1984 the vision remained 1/200 in the right eye and 20/50 in the left eye. The amount of subretinal fluid in the right eye had decreased further, and there was a small white subretinal scar where the RPE defect had been on 4 January (Fig.

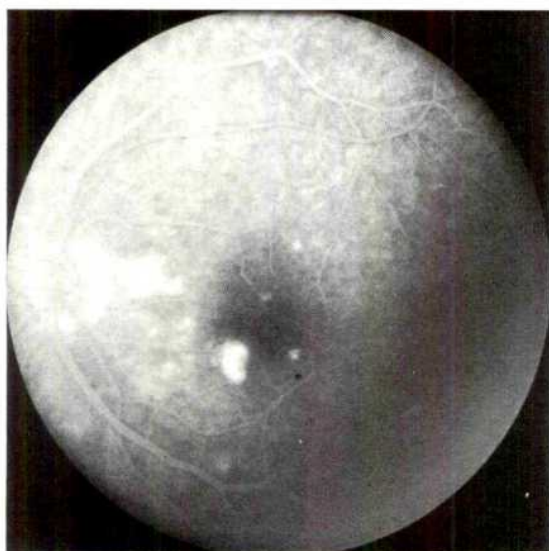


Fig. 8 Case 2. Left eye, 10 November 1983. Multiple transmission defects with slow leak present just temporal to the disc and early collection of dye inferonasal to fovea probably representing an RPE detachment.

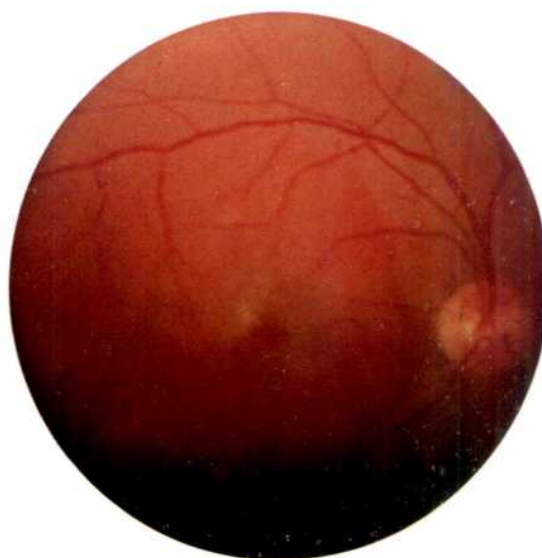


Fig. 9 Case 2. Right eye, 14 November 1983. Four days after Fig. 4, showing marked increase in subretinal fluid.

11). The scar was hypofluorescent on angiography (Fig. 12.). The left macula had a decreased amount of subretinal fluid just temporal to the disc.

On 27 March the patient's acuity was unchanged in the right eye but in the left eye had fallen to 20/200. In the left macula there was a neurosensory detachment over the RPE detachment on clinical examination. On angiography the RPE detachment stained more intensely, with blurring of its borders in the later phases, suggesting accumulation of dye in the overlying

subretinal space. The clinical examination and angiogram of the right eye remained the same.

By May 1986 vision had improved to 20/30 in the right eye and 20/25 in the left, with a flat pigmented macular scar present.

Discussion

These two cases appeared to represent a distinct entity apart from rips or tears in the pigment epithelium. They both occurred in middle aged men in the setting of severe central serous choroidopathy.

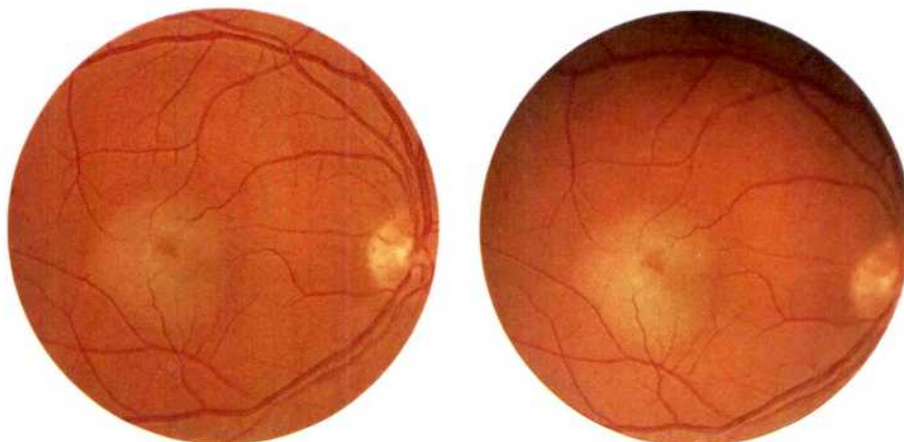


Fig. 10 Case 2. Right eye stereopair, 4 January 1984: $1\frac{1}{2}$ disc diameters opalescence of RPE with central RPE slit-like defect corresponding to area in Fig. 4 of RPE alterations.

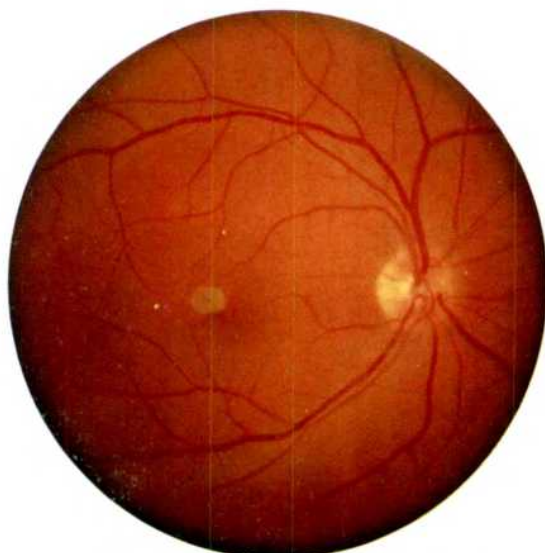


Fig. 11 Case 2. Right eye, 28 February 1984. 500 µm subretinal scar with hyperpigmented centre with no evidence of subretinal fluid, retinal oedema, blood, or exudate.

Neither case was associated with laser treatment, macular degeneration in the fellow eye, or with haemorrhage or exudate commonly seen in patients with tears or holes in the pigment epithelium. Both RPE defects were located in the perifoveal regions and were associated with visual loss. The RPE defects did not appear along the margin of an RPE detachment as is typical of an RPE rip²⁻⁴ but rather at the dome of the detachment. The edges of the defect were not retracted as is common in an RPE rip.¹ In both cases angiography showed early intense fluorescence at the site of the defect, which then progressively leaked dye into the subretinal space. The opalescence in case 2 appeared by stereobiomicroscopy to be an opalescent change in the RPE rather than a change in the transparency or debris on the photoreceptors. Since the defect was at the level of the RPE by stereobiomicroscopy, with visualisation of the choriocapillaris through it and an intact slit beam of the retina overlying it, it seemed that the RPE defect was in the same layer as the adjacent opalescent RPE. In patient 2 the defect occurred at a site which had tremendous leakage of dye into the subretinal space by previous angiography. This evolution suggests that the intense leakage of fluid led to weakening and eventual disintegration of the overlying RPE cells, causing 'RPE blow-out'. Although case 1 was not examined before the RPE blow-out had occurred, the position of the defect at the site of intense leakage at the apex of an RPE detachment implies its evolution was similar to that observed in case 2.

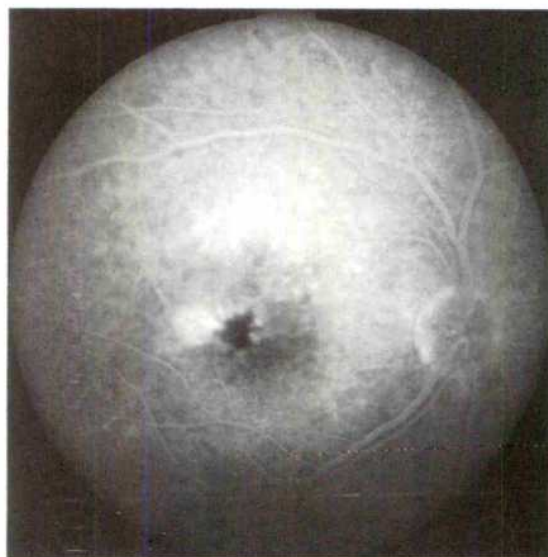


Fig. 12 Case 2. Right eye, 28 February 1984. Fluorescein angiogram reveals no leakage from areas of previously intense leakage.

Gass⁵ described a series of patients similar to ours. They had exudative retinal detachments with areas of serous RPE detachments and small pinpoint leaks in the RPE detachment that leaked into the subretinal space. Photocoagulation of the RPE detachment resulted in resolution of the RPE detachments. The majority of patients were healthy. Some of the exudative retinal detachments were bilateral, and some spontaneously resolved, as in our case 2. He considered his patients had a variant of central serous choroidopathy. DeBuestros *et al.*⁶ recently described three similar cases; however, none of these cases were described in association with holes in the RPE. Swanson *et al.*⁷ described cases of tears in the RPE which appeared to be related to traction from subretinal fibrosis in a setting of retinal detachment and in one case in association with a chorioretinal scar. Schatz⁸ described a patient similar to ours. He was a 58-year-old man with an RPE detachment in the macula and overlying subretinal fluid. There was a hole in the RPE and the choriocapillaries was visible through the hole. Argon laser was administered to the entire RPE detachment with improvement of vision from 8/200 to 20/30. Sunakawa and Tsukahara⁹ recently reported a case of an 'acute' RPE leak with an associated serous detachment treated with argon laser round the tear, resulting in retinal reattachment and improved vision.

Our cases were probably severe variants of central serous choroidopathy. It appeared that the intense leakage across the RPE caused the disintegration of these cells. There is both clinical¹⁰ and experimental¹¹

evidence that photocoagulation of the pigment epithelium causes restoration of the pigment epithelial barrier. Possibly these cases of unusually intense leakage might have a better prognosis if photocoagulation treatment is administered early in the clinical course. There is no anatomical defect that has been detected with central serous retinopathy¹² (and Gass JDM, personal communication), so that the leak through the RPE is presumably a functional defect. Whether the origin of this defect is choroidal or is a primary RPE disturbance is not clear. It is interesting that, although intense leakage was present in our case, no exudate accumulated in contrast to its frequent accompaniment with sub-retinal neovascularisation.

The authors thank Moira Burke, MD, for kindly allowing the examination of case 2.

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An evaluation of the NR-1000F Auto Refractometer in high refractive errors

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SUMMARY The manifest refractions of 37 high myopic and 16 high hypermetropic eyes in a total of 28 patients, aged 5 to 42 years, were determined on the Nikon NR-1000F Auto Refractometer. The data obtained were compared with the final clinical prescriptions for these eyes and analysed for degree of agreement for the spherical equivalents, sphere components, and cylinder powers and axes. The Auto Refractometer recordings for all the different refractive components were observed to skew towards more minus in the high myopic eyes but more plus in the high hypermetropes. The possible significance of these skewing patterns is discussed with reference to our earlier studies.

In an earlier study¹ on the Nikon NR-1000F Auto Refractometer (AR) we had carried out a systematic evaluation of the manifest (dry) refractions of 165 eyes with various types of refractive errors over a wide range of ages. A comparison of the AR readings with their corresponding manifest clinical refractive data had shown all the refractive components (spherical equivalent, sphere, and cylinder components) to skew strongly towards more minus (or less plus) on the AR. This error in manifest AR readings was greater in emmetropes, low hypermetropes, and low myopes. The skewing declined with increasing age over 40 years and was also significantly lower in aphakia and mixed astigmatism.¹

Further comparative studies between AR and clinical refractions were undertaken, both under manifest and cycloplegic conditions, in younger patients with low refractive errors.² This analysis substantiated our earlier suspicions that, in spite of the inbuilt automatic fogging system, the fixation target in the NR-1000F induces significant instrument myopia during manifest refractions in these patients.²

A definite difference had been observed in the skewing patterns on the manifest AR between eyes

with lower and higher refractive errors, though admittedly the number of eyes in the latter group was very few indeed.¹ In this paper we shall present our further experiences on the AR in eyes with high refractive error and discuss their significance in the context of our earlier studies.

Materials and methods

A total of 53 eyes in 28 patients were examined. The patients' ages ranged from 5 to 42 years (Table 1); 17 were males. None of the patients were paramedical or medical staff, and no patient was familiar with the Auto Refractometer. Only cases of myopia of more than -6 D and hypermetropia of more than +6 D were selected for this analysis.

All refractions on the AR were performed without the effect of any mydriatics or cycloplegics. The clinical refractions were either done similarly (manifest or dry), or if necessary under the effect of cycloplegics (homatropine 2% drops or atropine 1% ointment) or mydriatics (phenylephrine 10% drops), depending upon the age of the patient, in accordance with the guidelines routinely followed in clinical refractive practice. The final prescriptions to the patient were based on the objective clinical refraction data and the subjective acceptance, and these final prescriptions were then compared with the manifest AR printout data.

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Table 1 Distribution by age of 28 patients with high refractive errors

Age groups (years)	Type of refractive error (no. of patients)	
	High myopia	High hypermetropia
<10	2	1
11-20	12	2
21-30	4	1
31-40	1	4
41-50	0	1
Total	19	9

Table 2 Mean differences and standard deviations between Auto Refractometer and clinical refractive data in 53 eyes with high refractive errors

		Spherical equivalent (D)	Sphere component (D)	Cylinder component (D)	Cylinder axis (°)
Myopia (37 eyes)	Mean*	-0.53	-0.29	-0.52	4.42
	SD	±0.52	±0.52	±0.49	±3.53
Hypermetropia (16 eyes)	Mean*	+0.34	+0.29	+0.12	3.29
	SD	±0.38	±0.39	±0.20	±2.16

*The + and - signs indicate more hypermetropia and more myopia respectively on NR-1000F than clinical refraction data.

The clinical refraction and testing on the AR were not necessarily conducted by the same person. If both the examinations were carried out by the same person the clinical refraction was invariably done first, so as to obviate any possible examiner bias in the clinical refractive data.

The principles and steps of operation of the NR-1000F have been outlined earlier.¹ Further information on operating and maintenance is detailed in the manufacturer's instruction manual. A minimum of three AR readings was obtained for each eye tested. In accordance with the operating manual instructions, readings with a confidence value of less than 90 were rejected. The reading with the maximum confidence value in each eye tested was selected for comparison with the clinical data.

Table 3 Percentage agreement between Auto Refractometer and clinical refractive data of the various refractive components in 53 eyes with high refractive errors

	Spherical equivalent (D)			Sphere component (D)			Cylinder component (D)			Cylinder axis*	
	±0.25	±0.5	±1.0	±0.25	±0.5	±1.0	±0.25	±0.5	±1.0	Within 5°	Within 10°
Myopia (37 eyes)	37.8%	62.2%	83.8%	54.1%	83.8%	91.9%	32.4%	64.9%	89.2%	37.8%	51.4%
Hypermetropia (16 eyes)	37.5%	87.5%	93.8%	62.5%	87.5%	93.8%	68.8%	93.8%	100%	62.5%	87.5%

*No cylinder was detected in one of the testings in 16 of the 37 myopic eyes and in two of the 16 hypermetropic eyes.

Results

The mean difference and standard deviation between Auto Refractometer and clinical refractive readings for the various refractive components were evaluated separately for high myopia and high hypermetropia (Table 2).

The percentage agreements between AR and clinical data for these refractive components (spherical equivalent, sphere component, and cylinder powers and axes) were again analysed separately for myopic and hypermetropic eyes (Table 3).

Discussion

Much literature has accumulated on various types of subjective and objective autorefractometers.³⁻⁹ In view of conflicting claims to accuracy we had earlier carried out a wider study on the sophisticated Nikon NR-1000F Auto Refractometer, under both manifest and cycloplegic conditions.¹²

In our previous study on manifest refraction¹ the AR recordings skewed strongly towards more minus (or less plus), especially in the emmetropic, low myopic, and low hypermetropic eyes, more so below the age of 40 years. In contrast to this, a gentle skewing towards more plus (or less minus) was observed in the few cases of aphakia, mixed astigmatism, moderate and high hypermetropia, and in general all eyes in patients over 50 years of age.

In our present study the high myopic eyes still showed a consistent skewing towards more minus on the AR, though slightly lesser than the degree of skewing observed earlier in emmetropic, low myopic, and low hypermetropic eyes. On the other hand the high hypermetropic eyes showed an equally consistent skewing towards more plus on the manifest AR. We could not detect any significant variation for the different age groups in these skewing patterns in either the myopic or hypermetropic eyes studied, though admittedly all the myopes except one were less than 22 years old, and six out of the nine hypermetropes were over 25.

As eyes with high refractive errors should tend to exhibit a relative apathy towards accommodation, we had expected a significant reduction in the induced instrument myopia on the manifest AR for these eyes. As such, we are unable satisfactorily to explain this variation of skewing patterns on the manifest AR for the high myopic and high hypermetropic eyes, and this difference of the induced instrumental myopic error between them. It seems that the high myope still tends to accommodate, whereas the high hypermetropic eye truly shows a lack of accommodation, and this (as observed in aphakic eyes also) not only negates the inherent instrumental myopic error of this device but overneutralises it.

The determination of cylinder axes for these eyes on the AR proved as reliable and accurate as for all other types of refractive errors,¹² more so than in a subjective autorefractometer.⁹

Though the manifest AR data were fairly reliable for the high hypermetropes, in view of the induced instrumental myopia on this device even for the high myopic eyes it is recommended that the AR reading should be used only as a clinical guideline in such cases, and not prescribed as such straight away,

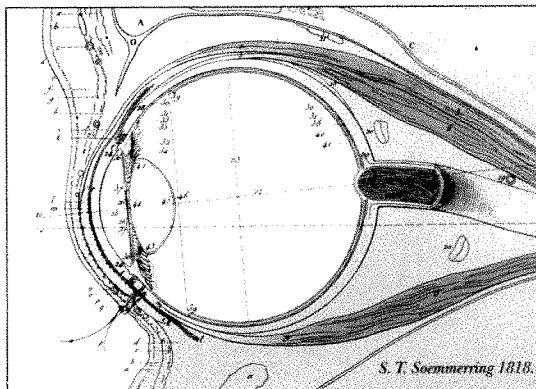
without at least carefully checking the acceptance subjectively.

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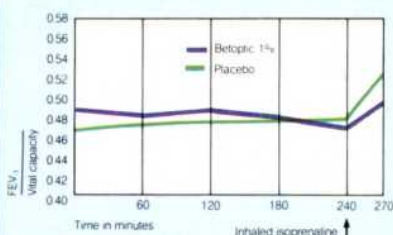
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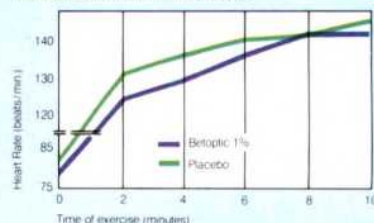
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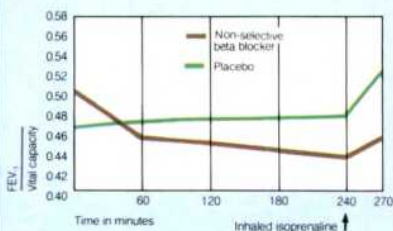


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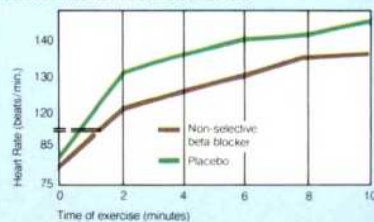
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Levator sling for Marcus Gunn ptosis

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SUMMARY A modified simple technique of sling operation is presented in 15 cases using the levator aponeurosis as the material for the sling as originally devised by Lemagne and Bemcher. The levator is cut behind the superior transverse ligament and the posterior part of the levator is cauterised and allowed to retract into the orbit. The horns are cut from behind forwards, and the levator, which is kept attached on the tarsal plate, is used to lift up the lid. This method eliminates the jaw winking phenomenon as well as lifting the lid.

Blepharoptosis with Marcus Gunn phenomenon presents a special surgical problem¹ for which there has so far been no clear-cut solution. Various surgical approaches suggested have included simple levator resection,² Fasanella Servat operation,³ total superior rectus transplantation,⁴ and the use of a bilateral sling^{5,6} after tenotomy and excision of levator. Lemagne and colleagues suggested frontalis suspension with the transposed levator palpebrae superioris and also presented some experimental models and human applications of this technique.^{7,8} Neuhaus⁹ described a case report with a similar procedure. The purpose of this paper is to describe the levator sling in a large series of cases of Marcus Gunn ptosis.

Material and methods

Fifteen cases of blepharoptosis with the jaw winking phenomenon were operated upon by this modified technique. The preoperative examination consisted of the assessment of the amount of ptosis, levator action, Bell's phenomenon, corneal sensations, and severity of jaw winking, together with taking of clinical photographs.

Jaw winking was assessed by determining the difference between the position of the upper lid margin in primary gaze and after movement of the jaw. Jaw winking was regarded as mild to moderate when the excursion of the lid margin on moving the jaw was up to the limbus. In more severe cases the scleral rim was shown. Levator action ranged from 4 to 8 mm (Table 1). Bell's phenomenon and corneal sensation were good in all cases.

Correspondence to SM Betharia, MD.

SURGICAL STEPS

The operation was carried out under general anaesthesia. The lid fold was marked at its proposed site by gentian violet. A skin and orbicularis deep incision was made. The upper skin muscle flap was further dissected upwards to expose the orbital septum, which was incised to release the pad of fat (Fig. 1). The fat was retracted and the levator was carefully dissected to determine the position of the superior transverse ligament (Fig. 2). Three white cotton thread stay sutures were passed through the aponeurosis distal to the superior transverse ligament and three proximal to it. The muscle was then divided just proximal to the superior transverse ligament (Fig. 3 and 4, showing the line of division of the levator muscle and its cut edges).

The medial and lateral horns were cut from behind forwards (Figs. 5, 6) so that the levator was made free at the level of superior transverse ligament and remained attached at the tarsal plate (Fig. 7). The posterior part of the levator was cauterised and allowed to retract totally in the orbit. The levator tendon with its attachment on the tarsal plate was used as the material of the sling for brow suspension.

The frontalis sling operation of Betharia¹⁰ was used with some modifications. The muscle was tied with 5-0 merselene suture and the two arms of the suture were brought out through the single brow incision

Table 1 Symptoms

Total cases	Mild to moderate jaw winking	Severe jaw winking	Amount of ptosis (mm)	Levator action (mm)
15	6	9	3-5	4-8

Fig. 1 Showing the levator aponeurosis and the herniation of the orbital pad of fat.

Fig. 2 Arrow depicts the position of superior transverse ligament.

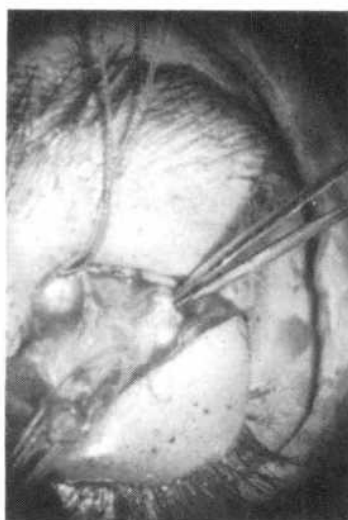


Fig. 1



Fig. 2

with the help of a Wright fascial needle (Fig. 8). Before pulling the levator tied with the merselene suture the lid fold was formed with interrupted 5/0 black silk suture (Fig. 9). Three knots were tied and the suture was buried. The skin incision was closed with 5/0 black silk suture (Fig. 10). Finally an inverted Frost suture was inserted (Fig. 11).

Results

The details of the results are given in Table 2. The postoperative follow-up of these cases ranged from six months to 15 months, average nine months.

Discussion

The two problems the surgeon faces in the correction of ptosis with the jaw winking phenomenon are the adequate correction of ptosis together with abolition

Table 2 Results

Good correction	Under correction	Lagophthalmos (average) (mm)	Disappearance of jaw winking	Lid fold formation
10	5	2	In all cases	Good

Fig. 3 Dark line indicates superior transverse ligament and dotted line represents line of incision.

Fig. 4 Arrows show cut edges of the levator.

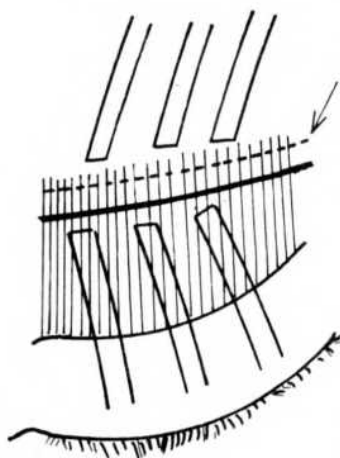


Fig. 3

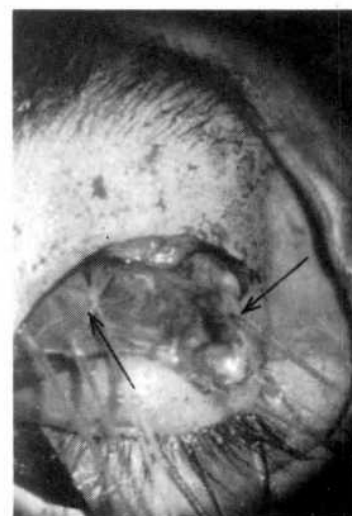


Fig. 4



Fig. 5 Cutting of medial horn of the levator.

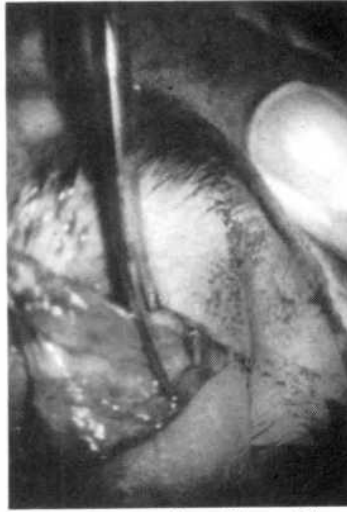


Fig. 6 Cutting of lateral horn of the levator.



Fig. 7 Levator aponeurosis with intact attachment at the tarsal plate which was subsequently used as sling.

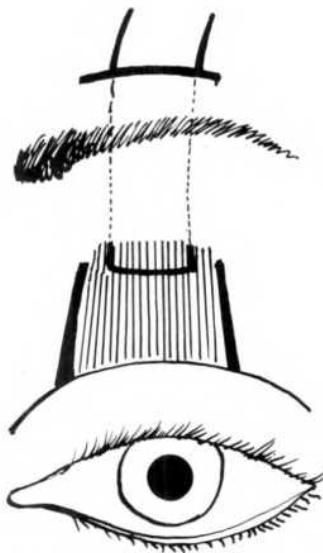


Fig. 8

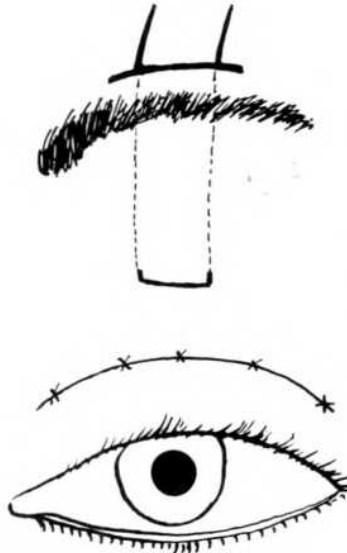


Fig. 9

Fig. 8 The levator aponeurosis with merselene suture being pulled up and brought out through the single brow incision.

Fig. 9 Closure of skin incision at lid fold site.

of the abnormal innervation causing the jaw winking. This latter should be effected by the division of the levator and its entire attachment to the lid. The unique feature of the present technique is the cutting of the muscle at the level of the superior transverse ligament. The other important features of this technique are the fact that the attachment of the levator was kept intact on the tarsal plate and the levator aponeurosis was used as the sling, thereby giving an even lift of the lid without any notching. The 5-0

merselene suture was very well tolerated and has not produced suture granuloma or infection so far.

We have noticed undercorrection in five cases. This finding has also been noted earlier by Beard,⁵ the probable reason being the blepharospasm in the early postoperative period as the patient is accustomed to a ptotic lid and is not willing to accept an open eye. It might be minimised by patching the opposite normal eye of the patient as suggested by Illif.¹¹

Fig. 10 Buried knot of merselene suture and closure of incision above the brow.

Fig. 11 The inverted Frost suture.

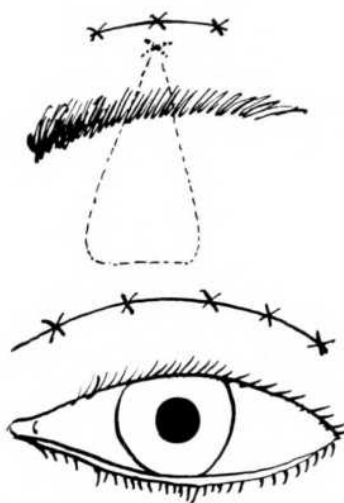


Fig. 10



Fig. 11



Fig. 12 Preoperative photograph showing ptosis in left eye.



Fig. 13 Preoperative photograph showing Marcus Gunn phenomenon.



Fig. 14 Early postoperative photograph showing good lids and absence of Marcus phenomenon.

We consider that slight overcorrection should be planned in all cases so that the final correction becomes cosmetically acceptable. The sling should be made taut so as to have the lid margin in a position of mild ectropion, and it should be kept at the level of the upper limbus. Lid lag which was marked in the beginning became less after a period of three months. Lagophthalmos was minimal in all cases.

This simple method of levator sling has given good results (Figs. 12 to 16) and has various advantages—

namely, total abolition of the Marcus Gunn phenomenon, maintenance of a good corneal lid margin, and a single stage operation because of bilateral slings with fascia lata material.

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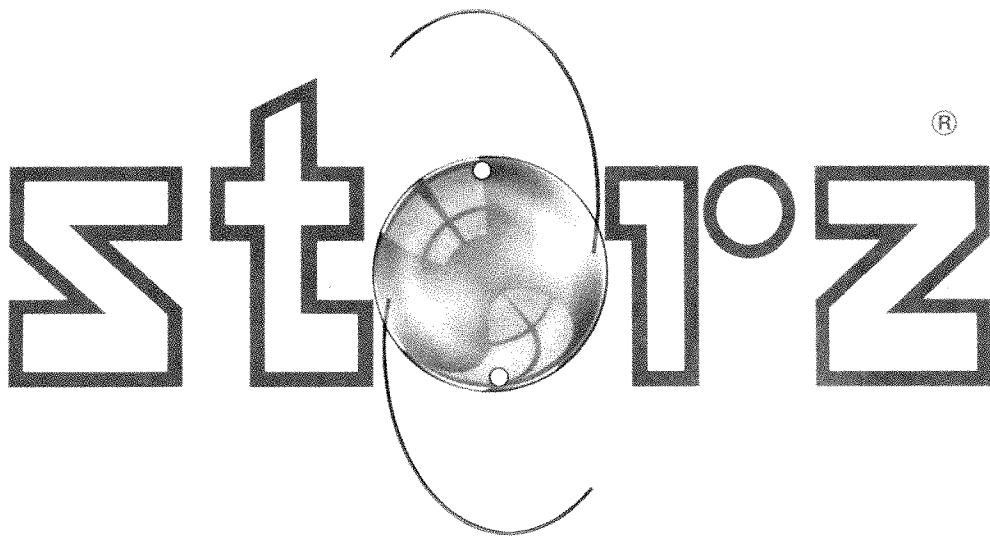
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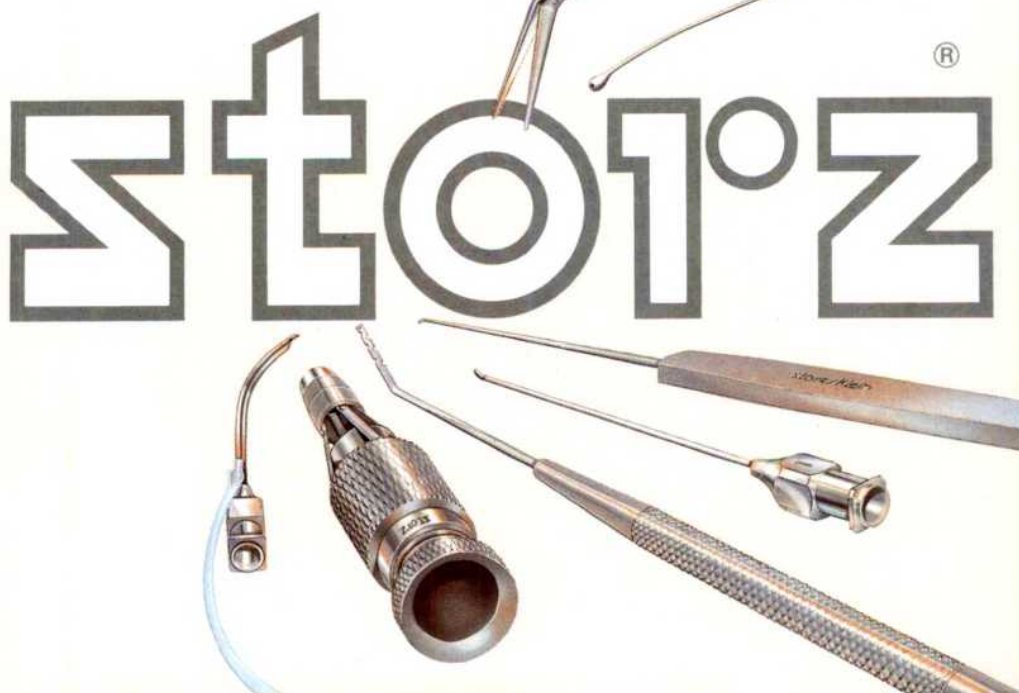


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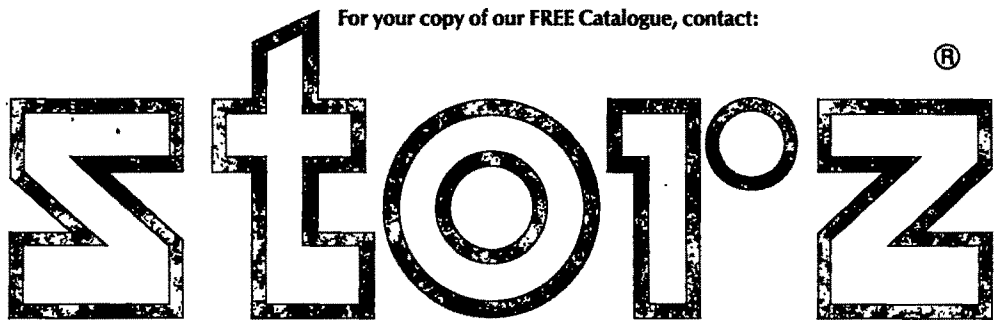


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Fig. 15



Fig. 16

Fig. 15 Late postoperative photograph showing good symmetry of lids with good lid fold and absence of Marcus Gunn phenomenon.

Fig. 16 Postoperative photograph showing lid lag.

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Mycobacterium chelonae infection of a corneal graft

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SUMMARY We present a case of *Mycobacterium chelonae* infection in a corneal graft. The chronic ulceration and stromal infiltration followed a well defined course and eventually responded to topical amikacin, though a further graft was required. Previous cases of keratitis due to the *M. fortuitum* complex are reviewed.

There is currently much topical interest in bacterial infections of the cornea associated with the use of extended wear soft contact lenses.¹ We report a case of a well defined keratitis in a corneal graft due to a very unusual organism, and associated with the wear of a Sauflon 85% soft contact lens.

Case report

In 1976 a 57 year old Caucasian woman with Fuchs's endothelial dystrophy and lens opacities underwent a left intracapsular cataract extraction. She was fitted with an extended wear contact lens (Sauflon 85%), but this was discontinued after two episodes of suppurative keratitis due to *Staphylococcus aureus*. In 1979 a left penetrating keratoplasty was performed because of stromal scarring and bullous keratopathy, and six months later another contact lens (Sauflon 85%) was fitted to correct her aphakia.

In May 1984 a stromal infiltrate was noted. It was within the graft next to the graft-host junction at 5 o'clock. She was treated with topical Betnesol-N (betamethasone and neomycin) once daily and chloramphenicol thrice daily, but one week later it had increased in size with thickening of the stroma and corneal oedema affecting the lower half of the graft. Corneal scrapings were taken for culture but were unfortunately lost in transit. Over the next two months more infiltrates appeared within the graft. These were white, fluffy, and stellate in appearance. It was thought that the cornea had decompensated owing to graft rejection and because she had little useful vision in the other eye (owing to a branch vein occlusion), a further penetrating keratoplasty was

performed in July 1984 with young donor material. A Stein intraocular lens was inserted at the same time.

Postoperatively the graft was clear and she was receiving topical dexamethasone three times a day. Six weeks later she presented with pain and redness of the left eye. She had a 1.5 mm ulcer at 9 o'clock on the graft-host junction, with several stromal infiltrates. There were cells in the anterior chamber but no hypopyon, and the intraocular pressure was raised on digital examination. She was admitted to hospital and corneal scrapings were taken for microscopy and culture, but no organisms were detected. She was treated with subconjunctival methicillin 125 mg and gentamicin 20 mg and topical methicillin and neosporin hourly. Additionally she received topical dexamethasone six times daily and oral acetazolamide 250 mg four times daily. After four days there was only limited improvement, and, in order to ensure that infection with pneumococcus or other streptococci was covered, the antibiotics were changed to topical penicillin hourly, chloramphenicol four times daily, and Polyfax ointment (containing polymyxin B and bacitracin) at night. Oral indomethacin 50 mg three times daily and ascorbic acid 500 mg three times daily were added in order to reduce the inflammation and to promote healing. The ulcer decreased in size, and she was allowed home one week later on this treatment, the penicillin being reduced to four times daily.

Two weeks later she was readmitted with a recurrence of pain in the left eye. On examination the ulcer had increased in size and there were several new infiltrates around the graft-host junction and a hypopyon. Corneal scrapings again revealed no organisms. She was treated with subconjunctival gentamicin 20 mg and cephaloridine 125 mg, topical

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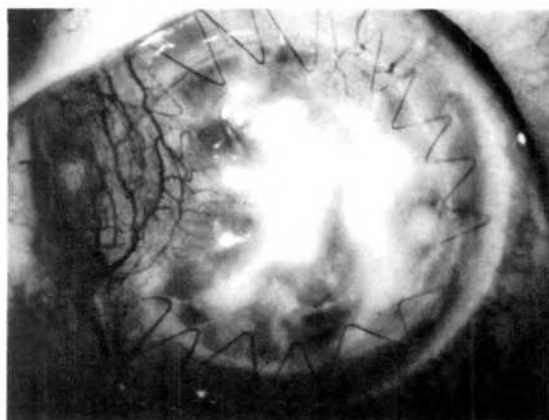


Fig. 1. Slit-lamp photograph of the left eye showing ulceration temporal to the conjunctival bridge flap and areas of stromal infiltration.

penicillin, and neosporin hourly and polyfax ointment at night. She continued with oral indomethacin 50 mg three times daily and ascorbic acid 500 mg three times daily. Later, oral tetracycline 250 mg four times daily was added. After 10 days there was no significant improvement, and a conjunctival bridge flap was fashioned to cover the area of ulceration, which was now approximately 2 mm in diameter. Further corneal scrapings were taken and inoculated into thioglycollate broth, and 11 days later an organism was isolated which was

initially reported as *Nocardia* sp. At this stage the eye was red with an area of ulceration temporal to the conjunctival flap. Smaller areas of ulceration with stromal infiltration were present along the graft-host junction between 12 and 5 o'clock (Fig. 1).

Two weeks later the organism initially reported as *Nocardia* sp. was identified by the reference laboratory as *Mycobacterium chelonae* sensitive to ethionamide and gentamicin but resistant to streptomycin, isoniazid, rifampicin, ethambutol, capreomycin, cycloserine, and pyrazinamide. All antibiotics were stopped for 72 hours and further corneal scrapings were taken. Ziehl-Neelsen staining revealed large numbers of acid-alcohol fast bacilli. (Fig. 2). There was no evidence of systemic mycobacterial infection, and a full blood count and chest radiograph were normal. Treatment with topical gentamicin six times daily and dexamethasone twice daily was begun and continued for two months. Initially the cornea cleared, but then several new areas of stromal infiltration appeared with two areas of ulceration (Fig. 3). Further corneal scrapings were taken for microscopy and culture. Again *M. chelonae* was isolated, and this isolate was found to be resistant to gentamicin in addition to the antibiotics previously tested. The organism was also tested against amikacin and found to be resistant. However, treatment was changed to topical amikacin four times daily and erythromycin ointment at night on the advice of Professor D. B. Jones (personal communication). Over the next month the ulcers

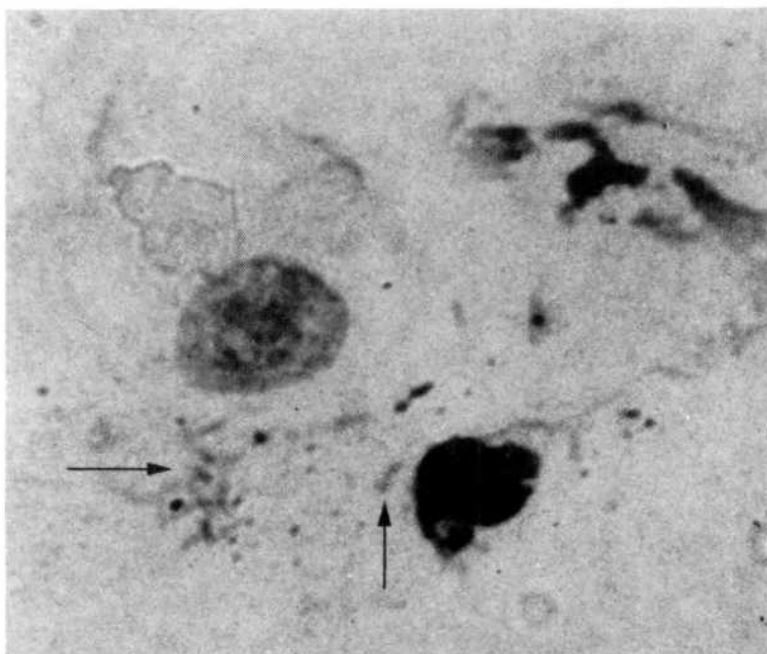


Fig. 2. Photomicrograph of corneal scrapings with Ziehl-Neelsen staining showing acid-alcohol fast bacilli (arrows).

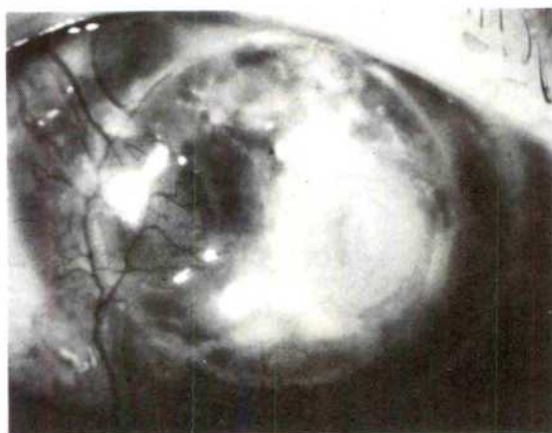


Fig. 3. Slit-lamp photograph of the left eye showing new areas of ulceration and stromal infiltration.

healed and the infiltrates cleared leaving a scarred, irregular cornea (Fig. 4).

She was continued on topical amikacin four times daily and dexamethasone twice daily for a full six months, and there was no recurrence of the ulceration or infiltrates. A further penetrating keratoplasty was performed in September 1985. Histology of the excised button showed a thickened epithelium with a chronic inflammatory infiltrate beneath Bowman's membrane. No granulomata were seen, but after staining with Ziehl-Neelsen stain a single acid-fast bacillus was found. She received amikacin four times daily for two months post-operatively. Eight months later she had a visual acuity of 6/18 with a clear graft (Fig. 5).

Discussion

In 1959 Runyon⁷ classified the atypical mycobacteria

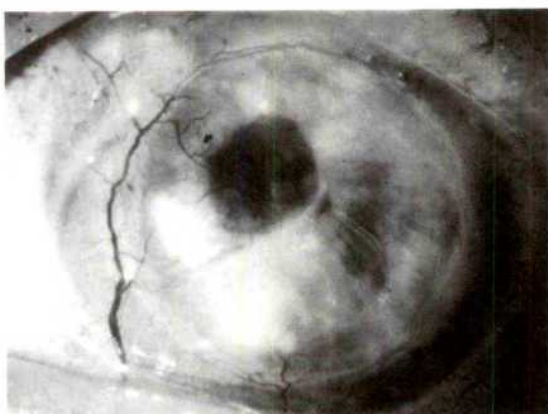


Fig. 4. Slit-lamp photograph of the left eye showing the healed but scarred and irregular cornea.

into four groups based on the pigmentation of colonies after exposure to light or darkness and their rate of growth on culture media. Group 4 contains the rapidly growing mycobacteria, including two species which are pathogenic to man, namely *M. fortuitum* and *M. chelonae*, which are often referred to collectively as the *M. fortuitum* complex. Owing to taxonomic confusion it is likely that *M. chelonae* has often been misidentified as *M. fortuitum* in the past. Therefore it may be reasonable to consider the reported cases of keratitis caused by these two organisms together as a single clinical entity.

Turner and Stinson described the first case of *M. fortuitum* keratitis in 1965.³ Since then a further 15 cases⁴⁻¹³ due to *M. fortuitum* and *M. chelonae* have been reported in the American literature. We believe that the present case is the first to be reported in the United Kingdom.

Keratitis follows corneal trauma after a latent period of two to eight weeks. In two reports^{10,13} there is a suggestion that contaminated ophthalmic instruments were responsible, though no organisms were cultured from them. The clinical appearance is similar to fungal keratitis, and in eight out of 17 cases (47%) this was the initial clinical diagnosis. An epithelial defect is associated with a white stromal infiltrate, often with satellite lesions and stromal radiations. Lazar *et al.*¹⁰ observed four early cases and described the 'cracked windshield' appearance of the cornea. The reaction in the anterior chamber varies from a few cells to a hypopyon. Posterior segment involvement has not been described. There was a long delay between presentation and diagnosis except in the three cases where the organism was suspected. During this period there was usually

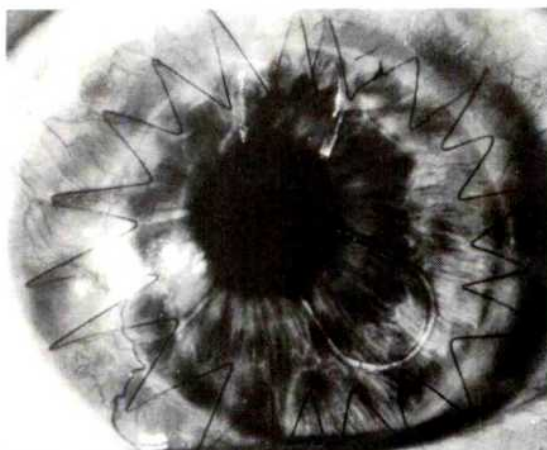


Fig. 5. Slit-lamp photograph of the left eye following the third penetrating keratoplasty.

intensive treatment with topical corticosteroids and a variety of antibiotics. The initial microbiological diagnosis was nocardia in six out of 17 cases (35%). This was probably because *M. fortuitum* and *M. chelonae* grow rapidly on ordinary culture media producing colonies in only three to four days, and because they may be easily decolourised on Ziehl-Neelsen staining. Moreover, if examined only by Gram stain, they may be dismissed as 'diphtheroids,' as happened in the case reported by Levenson and Harrison.⁴ The course of the disease is long and indolent, resolving in up to 13 months, usually leaving corneal scarring.

In 1970 Turner⁸ reviewed the first eight reported cases of ocular disease due to atypical mycobacteria including six cases of keratitis due to *M. fortuitum*. He also reported experimental studies which shed light on the pathogenesis of the condition. Rabbit eyes were inoculated with a suspension of *M. fortuitum* under various conditions. A progressive keratitis was not induced by inoculation into healthy corneas, but could be when the host defences were altered. This was accomplished by the use of topical corticosteroids, subconjunctival methylprednisolone, or intravenous cyclophosphamide. The presence of liquid petrolatum seemed to increase the virulence of the organism, suggesting that ointments should not be used in the treatment of infections caused by *M. fortuitum*.

Our case fits a well defined background for this type of keratitis but it is interesting to speculate on the possible source and time of infection. One possibility is that the organism was acquired on the occasion of the second penetrating keratoplasty. The progress of the infection may well have been assisted by the postoperative topical steroids. The period of six weeks between the graft and the development of the keratitis would fit well with the latent period of previous cases. Another possibility is that the organism was already present in the host cornea at the time of surgery and was responsible for the unusual stromal infiltrate that appeared in May 1984. If this is so, the organism may have been acquired as a complication of the use of the extended wear contact lens. These are well known to predispose to infectious keratitis from other more common bacteria.

M. chelonae is resistant to most antituberculosis agents. In the present case the organism was initially reported as sensitive to gentamicin but later became resistant, a fact which probably accounts for the initial improvement and subsequent relapse of the keratitis. Amikacin appears to be more effective both

in vitro and in vivo, and it is notable that the three cases treated with this drug responded relatively quickly, though one recurred on cessation of treatment.¹²

The following recommendations are made. There should be a high index of suspicion for *M. fortuitum* complex in any unusual keratitis, particularly those following corneal trauma and with multiple infiltrates underlying the ulceration. Staining for acid-fast bacilli should be performed, and suitable culture media for mycobacteria should be used routinely in such cases. Once the diagnosis is established, topical amikacin is probably the treatment of choice. This should be continued for a long period and well after the keratitis has resolved. If grafting is required, it should be carried out under appropriate antibiotic cover.

We acknowledge the help of Miss Sue Ford of the Western Ophthalmic Hospital and Mr M Savage of the Microbiology Department, St Mary's Hospital Medical School, who took and prepared the photographs; of Dr P A Jenkins of the PHLS Mycobacterium Reference Unit, Cardiff, who identified the organism and performed the sensitivity tests; and of Professor D B Jones of Baylor Medical College, Houston, who gave valuable advice about treatment.

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An association between 'Desert lung' and cataract – a new syndrome

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SUMMARY Sixteen cases of desert lung with cataracts were previously reported on, and an additional 14 cases have now been encountered from the same area of which 13 had cataracts. The association of cataract with desert lung was not commented on in the previous report, because it was thought to be coincidental. It now appears to be real rather than coincidental. Analysis of these 33 patients showed the following: none had significant clinical signs; x-ray findings were mainly those of micronodular miliary infiltrates; 88% were found to have cataracts; 85% were females. The frequency of cataract among patients over the age of 50 years coming to the hospital for eye problems was 26%. These figures showed a distinct relationship between desert lung and cataract in the Arabian desert. The causal relationship is not as yet clear, but 'tandoor' baking is suggested as the main factor.

The term 'desert lung' has been used to describe a non-occupational pneumoconiosis which is relatively common in desert areas. Its cause is prolonged, excessive exposure to atmospheric dust. Cases have been reported from the Sahara Desert,² Libyan Desert,³ and Negev Desert.⁴

Nineteen cases of desert lung from the Najd area (the central province of Saudi Arabia) have previously been reported from this centre,¹ of which 16 were found to have cataracts. Of this cataract subgroup 11 cases had undergone general anaesthesia for senile mature cataracts, while five cases were retrospectively diagnosed and had not been operated upon. An additional 14 cases of desert lung have now been encountered from the same region, 13 of which also have cataracts. This concurrent finding of cataracts was not commented upon in the previous report, because initially it was considered to be coincidental and the cataract due to the aging process. The frequent association of these two apparently unrelated diseases, desert lung and cataract, suggests the possibility of a common aetiology.

The aim of this study is to describe briefly the 29 patients who had both desert lung and cataracts and to suggest possible causes of this combination.

Material and methods

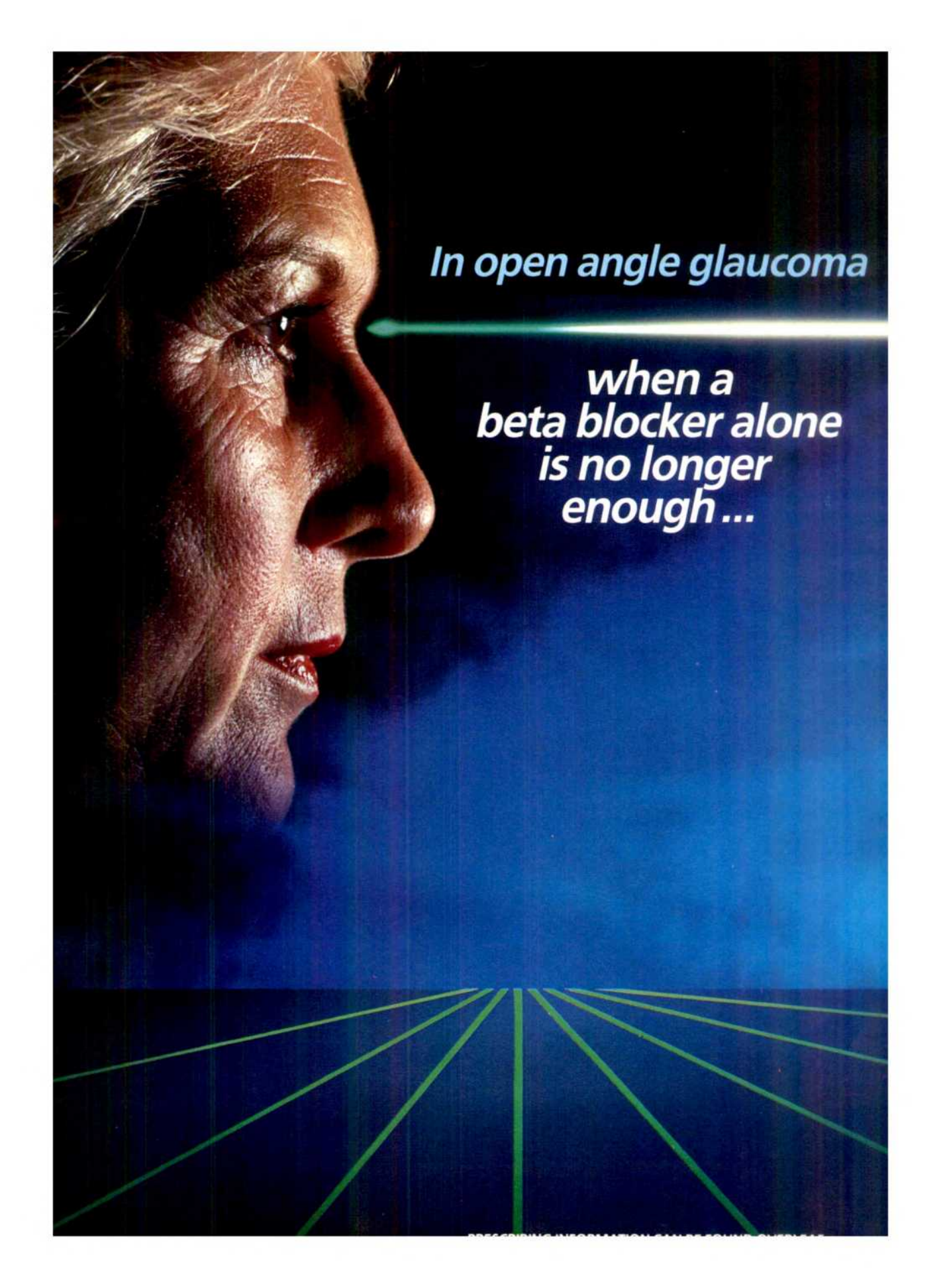
Cases. During a four-year period a total of 38 570

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chest x-rays were seen at King Abdul Aziz University Hospital in Riyadh, Saudi Arabia. Of these patients 4090 were over the age of 50 years, and among these were the majority of desert lung cases. Among these 4090 patients 33 cases were found to have desert lung (one case was 48 years old) and 29 of these 33 cases were found to have cataracts. Desert lung was diagnosed mainly by the presence of miliary or predominantly miliary mottling in chest x-rays in asymptomatic patients who lived in desert areas and had no occupational history. These patients showed normal results from relevant laboratory tests. (Three cases with desert lung were confirmed by lung biopsies.) The cases detected were then age matched with a control group from a similar geographic and ethnic background in the Najd area (central province of Saudi Arabia).

Controls. Six hundred and twenty-eight controls over the age of 50 years were obtained from a series of patients who attended the Ophthalmology Clinic and were referred for chest x-ray at King Abdul Aziz University Hospital in Riyadh. The chest x-rays of these patients showed no evidence of desert lung.

Statistics. Student's *t* test was used to determine the relationship between sex and mean age among desert lung cases and among controls. The χ^2 test was used to study the association between desert lung and sex of cases and controls. Fisher's exact test was used to compare cataract between cases and controls in



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Table 1 Sex distribution and mean age of cases and controls

Sex	Desert lung cases		Controls	
	Mean age (years)	Standard deviation	Mean age (years)	Standard deviation
Males	69.0	13.0	63.0	9.6
Females	59.2	6.0	60.5	8.2

Table 2 Association between desert lung and sex

Sex	Desert lung cases		Controls		Total	
	Number	Percent	Number	Percent	Number	Percent
Males	5	15	326	52	331	50
Females	28	85	302	48	330	50
Total	33	100	628	100	661	100

males and females. The incidence of desert lung was determined for the total survey population of 38 570 and for those over 50 years.

Results

FREQUENCY OF DESERT LUNG

Among 38 570 chest x-rays 33 cases of desert lung were identified (0.086%). Their ages ranged from 48 to 90 years; all but one were over 50 years. A frequency of 0.78% of desert lung cases over 50 years old was found.

AGE OF CASES AND CONTROLS

The mean age by sex of cases and controls is shown in Table 1. The mean age of female cases and controls was not statistically significantly different (Student's *t* test, $p > 0.05$). The mean age of male cases and controls was also not statistically different (Student's *t* test, $p > 0.05$). The male patients were about 10 years older than the female, but this result was not statistically significant (Student's *t* test, $p > 0.05$). The lack of significance may be due to the small number of male cases analysed.

SEX OF PATIENTS

The relationship of sex to desert lung is summarised in Table 2. Female sex was very strongly associated with desert lung ($\chi^2 = 16.9$, $p < 0.001$).

PRESENCE OF CATARACTS

The frequency of cataracts in female cases was 93% compared with 25% in female controls, a highly significant difference (Fisher's exact test $p < 0.001$). No significant difference was found in the frequency of cataracts between male cases and controls (Fisher's exact test, $p > 0.05$).

Table 3 Cataract morphology

Number of Cases	Cataract morphology
Right lens	
1	Anterior subcapsular (ASC) and posterior subcapsular (PSC)
1	Posterior cortical (PC) with posterior subcapsular (PSC)
16	Posterior subcapsular (PSC). Of this total, three had associated nuclear sclerosis (NS) and one had associated posterior cortical (PC)
5	Nuclear sclerosis (NS). Two cases had associated posterior subcapsular (PSC)
4	Complete opacification.
Left lens	
1	Anterior subcapsular (ASC) and posterior subcapsular (PSC)
3	Posterior cortical (PC). One case had associated posterior subcapsular (PSC)
13	Posterior subcapsular (PSC). One case was associated with posterior cortical (PC) and one with nuclear sclerosis (NS)
6	Nuclear sclerosis (NS). Two cases had associated posterior subcapsular (PSC)
4	Complete opacification

CATARACTS

Twenty-nine out of 33 patients with desert lung were found to have cataract; one case with bilateral corneal opacities is not included here. All cases of cataracts were bilateral. Cataract was defined as any lens opacity on or inside the lens not necessarily requiring operation.

MORPHOLOGY OF CATARACTS (Table 3)

The morphological description of two patients was confined to bilateral mature cataract in both lenses, and no further details were available. In three cases microscopic examination of lenses following extraction revealed homogeneous, structureless, eosinophilic material.

RADIOLOGICAL FINDINGS

The appearance on chest radiographs of desert lung cases showed (1) Uniform micronodular miliary infiltrates (Figs. 1A, 1B), which were dense and well defined (15 cases). Some had an appearance reminiscent of low grade alveolar microlithiasis but with a widespread distribution. (2) In addition to miliary infiltrates there was fine reticular shadowing which was evenly and equally distributed in both lungs (15 cases). (3) Miliary infiltrates with thickening of bronchial wall (eight cases). (4) Miliary infiltrates with Kerley B lines (three cases).

None of the patients had significant clinical pulmonary symptoms or signs. Relevant laboratory tests for all patients gave normal results. Seven patients had pulmonary function tests done; four

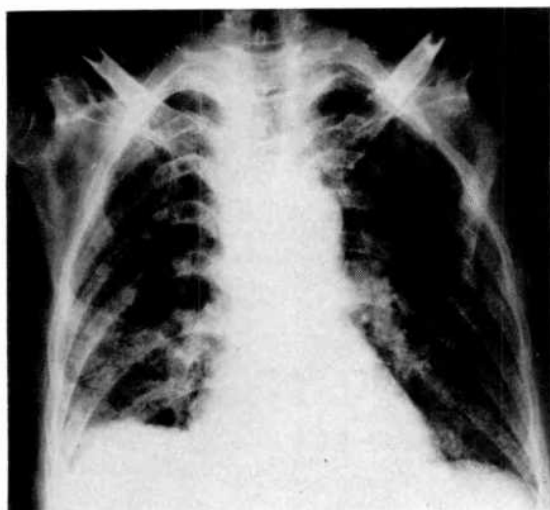


Fig. 1A Typical desert lung in a 62-year-old female patient showing diffuse micronodular pattern in both lungs.

were normal and three showed mild restrictive changes.

Transbronchial needle biopsy was performed in three cases and showed that the pulmonary miliary nodules seen on the chest radiographs were full of dust particles, being birefringent under polarised light (Fig. 2).

Discussion

Many physicians are not familiar with the disease of desert lung, so that most of these cases are misdiagnosed. Desert lung is mainly due to the high



Fig. 1B Close-up view of left lung.

silica content of the inhaled particles. As much as 70% is composed of fine particles of sandy dust. The prevalence of the disease among females is not clearly understood, but may be explained by their daily activities which involve cleaning, dusting, and herding, exposing them to dust and sand much more frequently than men throughout the years.

The disparity between the average age of males (69 years) and females (59 years) may be explained by

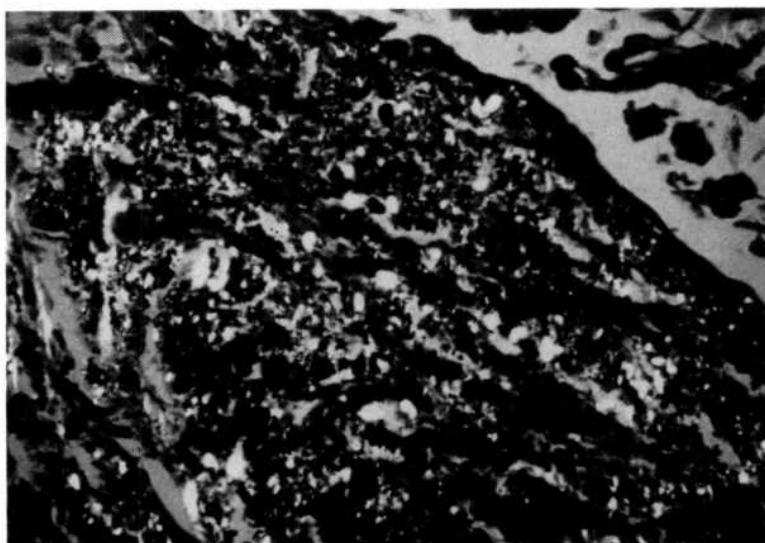


Fig. 2 Section of the lung nodule showing lung tissue and refractile dust particles. Polarised light.

Table 4 Association between desert lung and cataracts by sex

Sex	Desert lung cases						Controls					
	Males			Females			Males			Females		
	No	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cataracts	3	60	26	93	29	88	85	26	77	25	162	26
Non-cataracts	2	40	2	7	4	12	241	74	225	75	466	74
Total	5	100	28	100	33	100	326	100	302	100	628	100

the principal work activities of men, which result in far less exposure to fine particles of dust – though disparity may be false owing to the small number of male cases analysed. It was noted that older people showed advanced radiological changes, an observation which was not found by Hirsh *et al.*⁴ After taking into consideration that there is widespread exposure to atmospheric dust, the low incidence of the disease, particularly in male patients, and that all patients were asymptomatic, one can conclude that the atmosphere has a benign effect on the lungs. In two of the three patients with restrictive changes on the pulmonary function tests, chest radiographs showed the micronodular and reticular pattern. This might suggest that the micronodular pattern alone is more benign than micronodular and reticular infiltrates. However, further study of more cases is needed to verify such a correlation. The one patient with bilateral complete corneal opacities has not been included because cataract in this patient cannot be proved or excluded. Thickening of the bronchial wall was seen in eight patients, but this finding is relatively common among even young, healthy people in the region and is probably caused by the same dusty atmosphere.

The association of desert lung and cataract (Table 4) is highly significant. Furthermore, the actual frequency of cataracts among the population over the age of 50 years must be smaller because our sample represents patients from ophthalmology clinics and not from the general population. Correlation of severity of cataracts with the extent of pulmonary changes of desert lung has not been made in the present study.

A possible explanation for the concomitance of these diseases may be explained by the use of open fire of the 'tandoor' in the rural areas. A tandoor is a one-metre high, barrel-like apparatus made of potter's clay, erected vertically above the ground and in which a fire is lit. As the tandoor is used daily for baking in the rural area, the women have to lean over and look inside it, thus exposing themselves to long periods of high temperatures and hot air inhalation. Exposure to tandoor heat is quite intense, and,

since the women have frequently to check the tandoor, they sometimes have strands of hair or even eyelashes singed. This persistent exposure to intense heat may have a dual effect: (1) damage to respiratory cilia and the resultant predisposition of the lungs to atmospheric dust deposition; this might also explain the prevalence of desert lung in female patients. (2) development of cataracts as a consequence of the long exposure of the eyes to high temperatures, a condition similar to 'glassblower's cataract.'

It is well known that exposure to high temperatures which do not produce any significant abnormality in the rest of the body will produce pathological effects on the eye. Infrared injury absorbed by the iris is transmitted to the lens and causes cataracts.⁵ The reasons for this are two-fold: (1) heat in the anterior segment of the eye, particularly on the pigment of the iris, will induce metabolic changes that are deleterious to the lens; (2) as the lens is avascular, dissipation of heat takes place from it at a much slower rate than from the rest of the body.

The morphological prevalence of posterior subcapsular cataracts in these patients is consistent with chronic exposure to heat and similar to the chronic exposure of infrared radiation by glassblowers and furnace workers, which causes posterior subcapsular cataracts.⁷

I would like to thank Dr Surur Shahozad, consultant ophthalmologist, University Hospital in Riyadh, for helping in the retrospective analysis of the incidence of cataracts; Dr Abdul Hafid, professor of pathology, for providing the histology section; and Professor Whitehouse for his helpful advice. I gratefully acknowledge the assistance of Dr Theresa L. Sweeney, of the Department of Community and Family Medicine, King Saud University, for her statistical advice. I also thank the radiologists at both university hospitals in Riyadh for their cooperation in this study.

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A comparison of the effects of oral nadolol and topical timolol on intraocular pressure, blood pressure, and heart rate

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SUMMARY We compared the effects of oral nadolol 20 mg once daily and topical timolol 0.25% twice daily on the intraocular pressures of 22 glaucoma suspects, in a 12 week double-masked crossover study. Both nadolol and timolol reduced intraocular pressure ($p < 0.001$). The reductions in intraocular pressure did not differ significantly after two weeks and four weeks of treatment. Nine of these subjects underwent treadmill exercise tests in order to compare the effects of nadolol and timolol on the cardiovascular system. The effects of the two treatments on blood pressure were comparable, but nadolol caused a significantly greater reduction in heart rate than timolol at rest ($p < 0.05$). Nadolol reduces intraocular pressure effectively and may prove a useful alternative treatment for chronic simple glaucoma.

Introduced in 1979 for the treatment of chronic simple glaucoma, timolol offered a relatively low frequency of local side effects when compared with established topical treatment. The ease of administration of a long-acting oral beta blocking agent might further improve patient compliance. Nadolol is a non-selective beta blocker with a plasma half-life of 17-23 hours. It reduces intraocular pressure over a 24-hour period when applied topically to the eye in a 2% solution,¹ but habituation appears to occur within one month.² When administered systemically in doses of 10-80 mg once daily it reduces intraocular pressure,^{3,4} and a reduction can be obtained for at least 24 months on long-term therapy.⁵ We compared the effects of oral nadolol and topical timolol, on intraocular pressure, blood pressure, and heart rate in a 12-week double-masked crossover study.

Patients and methods

Twelve male and 12 female patients, aged 47-78, with normal visual fields were recruited from a glaucoma clinic. These patients were thought to be at risk of developing glaucoma because of their intraocular

pressures, a family history, or the appearance of their optic discs. Exclusion criteria were: confirmed open angle or closed angle glaucoma, any visual field defect, visual acuities of less than 6/12, corneal disease, a history of ocular surgery, asthma, chronic obstructive airways disease, cardiac failure, renal dysfunction, or current therapy with a beta blocking agent.

Ethical approval was obtained from the hospital ethics committee. All subjects gave written informed consent and underwent a pretrial physical examination (including an electrocardiogram for those subjects undergoing exercise tests). All subjects had their visual fields checked with a Goldmann perimeter (Armaly technique⁶) to ensure that they were normal. Those on ocular hypotensive treatment had their case histories and visual fields reviewed by an independent observer before their medication was stopped at least two weeks prior to the trial.

This double-masked crossover study lasted 12 weeks. Of 24 subjects entered in the trial one was withdrawn because of an electrocardiographic abnormality found in preparation for the exercise test, and one was withdrawn because of malaise and lethargy while on timolol. The subjects were randomly allocated into two groups. There were 13 subjects in group 1 and nine in group 2. Throughout

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the trial the subjects took one tablet once a day, and instilled one drop twice a day in each eye. Group 1 received nadolol 20 mg tablets once daily and placebo drops twice daily for four weeks, followed by a four-week wash-out during which they received placebo drops and placebo tablets. After crossover they received timolol 0.25% drops twice daily and placebo tablets once daily for four weeks. Group 2 was started on timolol drops (and placebo tablets) for four weeks, and after a four-week wash-out and crossover they continued with nadolol tablets (and placebo drops).

Intraocular pressures were measured at baseline and then fortnightly for 12 weeks. All the intraocular pressure measurements were made within 10 hours of dosage by the same investigator (GRD) at the same time of day for each subject (to within 25 minutes). Subjects had their visual fields reassessed at the end of the trial if their intraocular pressures rose to levels higher than those found at the time of their referral to the glaucoma clinic.

The cardiovascular effects of nadolol and timolol were studied, and 10 subjects underwent symptom-limited treadmill exercise tests on three occasions: off treatment, on nadolol, and on timolol. One of the 10 subjects was unable to complete the treadmill tests as she sustained a back injury at home. There were five subjects in treatment group 1 and four in treatment group 2. The duration of the test off treatment was taken as the end point of further tests during each treatment period. Heart rate and blood pressure data immediately after peak exercise are reported.

Log transformation of the data on intraocular pressures helped to reduce the skew towards zero, and the analyses are therefore based on log transformed data. The averages of two eyes are used in order to minimise imprecision. There is no consistent evidence of skew in the cardiovascular data such as would suggest the need for a log transformation.

The statistical significance of the changes in intraocular pressure, blood pressure, and heart rate on each treatment was assessed by paired *t* tests comparing values on treatment with preceding baseline values (that is, the readings at 0 or 8 weeks).

The comparison of changes in intraocular pressure, blood pressure, and heart rate between the two treatments was performed by the method of Hills and Armitage.⁷ The difference in effect between treatments was assessed by an unpaired *t* test comparing period differences in the two random groups (group 1: nadolol first, *n*=13; group 2: timolol first, *n*=9), with corresponding analyses for period and interaction effects. However, when the efficacy of the washout period was examined by paired *t* tests, the intraocular pressure results for right eyes after four weeks of washout were significantly higher than

at week 0 (*p*<0.05). The intraocular pressure crossover comparisons were therefore more validly based on increments from the preceding baseline values. When this was done there was no evidence of corruption by period or interaction effects. Confidence intervals are given for the difference in effect between treatments.

Results

INTRAOCULAR PRESSURES

Table 1 summarises the distribution of intraocular pressure before treatment (weeks 0 and 8) and after two and four weeks of treatment with timolol and nadolol. Appropriate summary measures for the log normal distribution are given, the geometric mean, and fitted 2.5 and 97.5 centiles. Both treatments produced a highly significant reduction in intraocular pressure (*p*<0.001). There was no significant evidence of any difference in effectiveness between the treatments. After two weeks of treatment the values on nadolol were +13% higher than on timolol, taking baseline values into account. A 95% confidence interval for this difference is from -13% to +47%. The corresponding difference at four weeks was +8%, with a 95% confidence interval from -3% to +36%.

Table 1 Summary statistics for intraocular pressure (mmHg), off treatment, on timolol and on nadolol; based on 22 subjects, eyes averaged

	Geometric mean IOP	Fitted 2.5 and 97.5 centiles	
Off treatment, week 0	22.5	13.6	37.3
Off treatment, week 8	21.9	12.6	37.3
After 2 weeks' timolol	16.5	11.2	24.5
After 4 weeks' timolol	16.9	10.1	26.5
After 2 weeks' nadolol	17.7	10.1	30.7
After 4 weeks' nadolol	17.7	10.8	29.1

HEART RATE AND BLOOD PRESSURES

Table 2 summarises the haemodynamic effects in the nine patients tested. On nadolol the heart rates at rest and after exercise were greatly reduced. The corresponding reduction on timolol was approximately one-third as great and did not reach statistical significance. The reduction in resting heart rate on nadolol was significantly greater than that observed on timolol (*p*<0.05); the corresponding difference after exercise approached significance.

The two drugs produced comparable effects on blood pressure; with a decrease in systolic blood pressure, most marked after exercise.

Table 2 The haemodynamic effects of nadolol and timolol in nine subjects. Serial changes from baseline values are assessed by paired *t* tests

	At baseline (SD)	On nadolol (SD)	On timolol (SD)	Crossover analysis	
				Mean difference nadolol minus timolol	(95% confidence interval)
Heart rate, bpm					
Rest	79(12)	57 (7)**	73(11)	-16	(-27 to -6)
Exercise	110(27)	81(15)*	101(23)	-20	(-40 to +1)
Systolic blood pressure, mmHg					
Rest	147(22)	137(23)	133(22)	+3	(-13 to +19)
Exercise	181(20)	156(19)***	163(11)***	-9	(-21 to +4)
Diastolic blood pressure, mmHg					
Rest	88(12)	86(12)	86(10)	-0.2	(-8 to +8)
Exercise	94(13)	85 (7)	87(12)	-3	(-12 to +7)

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, else $p > 0.05$. bpm = beats per minute.

Discussion

To our knowledge this is the first controlled study (the subjects acting as their own controls in this crossover study) comparing the effects of oral nadolol and topical timolol on intraocular pressure and on the cardiovascular system. Nadolol produced a significant reduction in intraocular pressure when administered systemically, and this effect is of the same order of magnitude as that produced by timolol. This confirms the results of a previous open study.³ In our study the drop in intraocular pressure after treatment with oral nadolol for two weeks and four weeks is very similar to that obtained by Rennie and Smerdon (at days 1 and 8).⁴ Our observations were all made within 10 hours of dosage, and we are therefore unable to comment on the 24-hour control of intraocular pressure.

The effects of nadolol and timolol on intraocular pressure do not differ significantly, but, if the maximum effects of the two drugs are compared at two weeks, we find that the intraocular pressures on nadolol are 13% higher than those on timolol. The sample size in this study is not large, and we cannot exclude the possibility of a clinically important difference in the effects of the treatments, but our data are consistent with the two treatments being equally effective.

There is a much greater reduction in heart rate on nadolol, though the effects of nadolol and timolol on blood pressure are similar. This suggests, that, when there is a relative contraindication to the use of beta blocking agents, nadolol will have to be used with caution.

Nadolol is one of a number of beta blocking agents that have been studied with a view to their use

in chronic simple glaucoma. The most widely investigated is timolol, which has for some time been established as the first line of treatment. Any proposed alternative glaucoma therapy should at least equal timolol in terms of efficacy, patient compliance, and side effects. In chronic simple glaucoma, whenever beta blockade is not contraindicated and the patients find it difficult or inconvenient to instil drops (or there is some other problem with compliance), nadolol should prove to be a safe and effective treatment.

We are grateful to Dr Newcombe, of the Department of Medical Computing and Statistics, University of Wales College of Medicine, for his help and advice in the design and analysis of this study.

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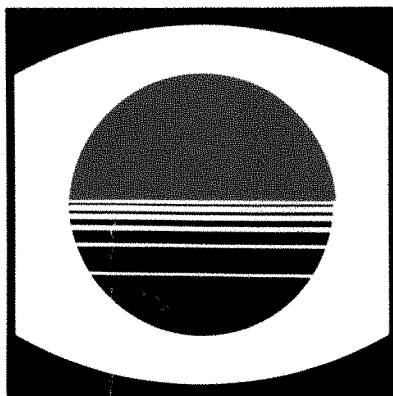
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Sport associated eye injury: a casualty department survey

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SUMMARY A survey was performed of all patients attending the combined Glasgow Eye Infirmary and Western Infirmary Eye Casualty Department with sports injuries. During an 18-month period a total of 246 patients presented with such injuries. Football was responsible for 110 (44.7%), rugby for 24 (9.8%), squash for 19 (7.7%), badminton for 16 (6.5%), and skiing for 9 (3.7%), and 68 (27.6%) were caused by other sports. One hundred and sixty-two patients (65.8%) had superficial or surrounding soft tissue injuries, 54 (22%) had more severe anterior segment damage in the form of hyphaema or traumatic uveitis, 17 (6.9%) had retinal damage manifest as oedema or retinal tear with or without detachment, and two (0.8%) suffered severe disruption of the globe with subsequent loss of the eye in each case. Forty-six (18.7%) required inpatient care and 200 (81.3%) were treated as outpatients, of whom 104 required at least one follow-up appointment (42.3% of the total). I conclude that with increasing time available for leisure activities there has been a parallel increase in sport associated eye trauma.

Keeping fit by participating in sport is becoming more popular in all age groups. This has undoubtedly resulted in an improvement in general health, but it has also caused an increase in sporting injuries which has been termed the 'unthwarted epidemic'.¹ Despite the eye's protected position and its protective reflexes it is still vulnerable to injury, especially in sports which involve a small ball.² Squash racquets has aroused much interest for this reason.³⁻⁵ Badminton is also recognised as a racquet sport in which ocular injury may occur.^{4,7-9} Golf,¹⁰ hockey,^{11,12} tennis,¹³ and swimming¹⁴ have all been recorded as a source of eye trauma. Boxing by its very nature may cause facial and eye injuries.^{8,15-17} The problem of sport associated eye injury has been recognised and attention is now concentrated on methods of protection from and prevention of such injuries.^{18,19}

The aim of this study was to determine the incidence, mechanism, and outcome of eye injuries associated with various sports in the west of Scotland.

Materials and methods

All casualty records for the 18-month period 1 January 1985 to 30 June 1986 were examined retro-

spectively. The records of all sport associated eye injuries were identified, and details of age and sex, mechanism of injury, extent of injury, and outcome were all noted along with the sport involved. Despite its being a retrospective study the details of mechanism of injury were well documented. However, one aspect—namely, that of eye protection in use—was poorly recorded.

Results

A total of 246 cases of sport-associated eye injuries were identified. There were 213 (86.6%) male patients and 33 (13.4%) female patients. The average age was 24.8 years, range of 6-66 years (Fig. 1).

SPORT INVOLVED

The sport involved was association football in 110 cases (44.7%), rugby football in 24 (9.8%), squash racquets in 19 (7.7%), badminton in 16 (6.5%), skiing in 9 (3.7%), tennis in 7 (2.85%), swimming in 7 (2.85%), cricket in 6 (2.4%), golf and hockey in 3 (1.2%) each, and other sports in 42 (17.1%) (Table 1). Other sports included combat sports such as boxing, wrestling, karate, and judo; also in this group were netball, basketball, table tennis, jogging, horse riding, fishing, darts, water

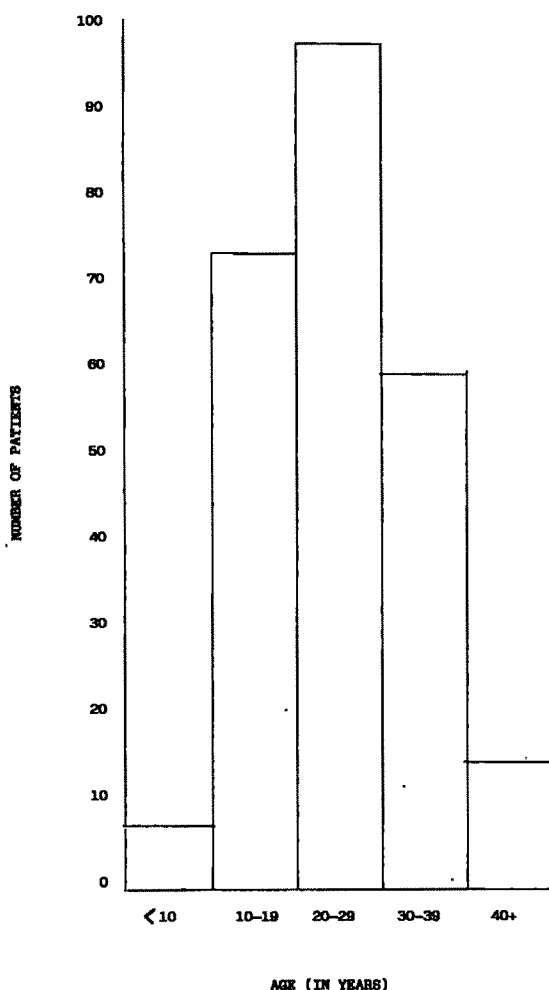


Fig. 1 Age distribution of injured patients.

skiing, sailing, shinty, and handball. No patient received an injury to more than one eye. One patient presented on two separate occasions during the study period, on each occasion with a superficial injury incurred while playing rugby football.

AETIOLOGY

The mechanisms of injury were well documented and may be divided into the following five categories (Table 2): ball to eye contact; racquet or bat to eye contact; body to eye contact; introduction of a foreign material into the eye; the participant may fall over, striking the eye or head.

Ball contact accounted for 118 (48%) of all injuries. This mechanism was most common in those sports played with a small ball, in particular the racquet sports (squash, badminton, tennis), golf, and cricket; however, the majority of football injuries were also sustained in this way. Body contact, either

Table 2 Mechanism of injury in relation to sporting activity

	Ball	Body	Racquet/ bat	Foreign body	Fall
Association football	65	35	NA	9	1
Rugby football	3	19	NA	2	—
Squash	15	—	3	1	—
Badminton	14	—	2	—	—
Skiing*	NA	2	NA	—	4
Tennis	7	—	—	—	—
Swimming	NA	5	NA	2	—
Cricket	5	—	1	—	—
Golf	2	—	—	1	—
Hockey	—	—	2	1	—
Others	7	11	—	20	2
Total	110 (48%)	72 (29.3%)	10 (4.2%)	36 (14.6%)	7 (2.8%)

*Three skiers had ultraviolet injury. NA=not applicable.

Table 1 Type of eye injury in relation to sporting activity

	Periorbital injury	Conjunctival haemorrhage or laceration	Corneal abrasion	Traumatic uveitis mydriasis	Hyph- aema, iris tear	Hyph- aema, angle recession	Diffuse blunt trauma	Retinal oedema	Tear, detach- ment	Scleral rupture	Intra- cranial	Total
Association football	19	6	44	11	9	2	7	10	2	—	—	110
Rugby football	1	8	8	3	1	—	2	—	—	1	—	24
Squash	4	2	5	3	3	1	—	1	—	—	—	19
Badminton	3	—	3	4	2	4	—	—	—	—	—	16
Skiing	2	1	3	1	—	—	—	1	—	—	1	9
Tennis	1	1	2	—	—	2	—	—	—	—	—	7
Swimming	—	3	4	—	—	—	—	—	—	—	—	7
Cricket	5	—	1	—	—	—	—	—	—	—	—	6
Golf	1	—	1	—	—	—	—	—	1	—	—	3
Hockey	1	—	1	—	1	—	—	—	—	—	—	3
Others	7	6	19	2	5	—	—	—	1	1	1	42
Total	44	27	91	24	21	9	9	12	5	2	2	246

with self or opponent, accounted for 72 (29.3%), and entry of a foreign body into the eye was responsible for a further 36 (14.6%). Racquet or bat contact was responsible for 10 injuries (4.1%), and a fall striking the head or eye accounted for another 7 (2.8%). The remaining 3 (1.2%) injuries were all caused by ultraviolet light in skiers, leading to corneal epithelial oedema ('snow blindness') or herpetic keratouveitis.

OCULAR DAMAGE

The majority of injuries were superficial (65.8%), but a significant number of patients had intraocular damage (Table 1). Forty-six patients (18.7%) required admission to hospital, though one refused admission and further follow-up. The remainder were treated as outpatients; 96 (39%) were seen only at the initial presentation with a further 104 (42.3%) requiring outpatient follow-up.

There were 91 cases (37%) of corneal abrasion, and, of these, three subsequently required treatment for recurrent corneal erosion. In one case corneal damage was caused when lime from the side markings on a football pitch entered the conjunctival sac. There was delay in seeking medical advice, and the resultant corneal ulcer was resistant to treatment.

Uncomplicated traumatic uveitis occurred in 24 cases (9.8%) and hyphaema in 30 (12.2%), of which nine (3%) subsequently displayed angle recession. Of these cases six had a significant rise in intraocular pressure, four settled spontaneously, but one required trabeculectomy and the other is maintained on medical treatment. Two patients had a second bleed while in hospital.

Nine patients (3.7%) with severe, diffuse, blunt trauma involving both the anterior and posterior segments had various combinations of hyphaema, angle recession, cataract, vitreous haemorrhage, retinal haemorrhage, retinal tear, retinal oedema, and optic nerve damage. It is noteworthy that this group did well, eight retaining acuity of 6/12 or better. One eye had no perception of light for 24 hours following injury, but this improved to 6/12 within 48 hours. The others displayed persisting evidence of trauma in the form of vitreous debris, abnormal retinal pigmentation, or posterior subcapsular lens opacities. One eye ended up with an acuity of 3/60 due to optic nerve damage.

Three retinal detachments involving the macula were all successfully reattached, but acuities remained poor at 6/24, 6/36, and counting fingers. Two eyes had symptomatic retinal tears which were successfully treated with cryotherapy, with or without plombage; both retained 6/6 vision. Two eyes (0.8%) had extensive scleral rupture, both of which culminated in enucleation of the affected eye. One patient had got an opponent's finger in the eye while

playing rugby and the other was involved in a freak whiplash accident while water skiing. Two patients presented because of complications of intracranial damage; one had a transient hemianopia and the other a fourth nerve palsy following blunt head trauma.

Ocular motility problems arose in three patients. Two had severe periorbital bruising, but no fracture could be demonstrated either radiographically or clinically. Both patients gradually improved over the ensuing months, though one still had asymptomatic limited adduction of the affected eye. One fourth nerve palsy recovered spontaneously. There were two blowout fractures, neither of which suffered diplopia or enophthalmos, though one had surgical emphysema.

PROTECTION

Specific mention of protective eye wear was made in only two cases. These were swimming goggles in both instances, and it was these goggles which were responsible for the eye injury, having slipped out of wet hands into the eye. Of the three skiers with ultraviolet injury one had lost his sun glasses and the other two had omitted to wear them. There was no record of ultraviolet protection in the other skiers. Five patients were wearing glass corrective lenses which had shattered, all the patients sustaining superficial lacerations or abrasions to the lids or cornea. Three patients suffered corneal abrasions while wearing contact lenses.

FINAL ACUITIES

The final visual acuity was 6/6 or better in 200 cases (81.3%). Only two eyes were left with acuities of less than 6/60, a further two eyes were enucleated, and one patient was lost to follow-up (Table 3).

Table 3 Final corrected visual acuity

Final visual acuity	Eyes (%)
6/6 or better	200 (81.3%)
6/9-6/12	37 (15.1%)
6/18-6/60	4 (1.6%)
Less than 6/60	2 (0.8%)
Enucleated	2 (0.8%)
Lost to follow-up	1 (0.4%)

Discussion

Sport associated eye injuries occur during a variety of different sporting activities. The mechanisms by which they occur may usefully be divided into five groups: ball contact; racquet or bat contact; body contact; foreign body; and falling over. Ball contact accounted for the majority of injuries overall in this

series and was particularly common in the racquet sports (squash, badminton, tennis). The close relationship between the size of the squash ball and the orbital aperture has roused particular interest in this activity as a cause of serious eye injury,^{2,4,5} though racquet and body contact are also common.^{3,6,7} Badminton, golf, tennis, and hockey usually involve injuries caused by ball or racquet/bat contact,^{4,7,9-12,20} whereas body to eye contact is usually responsible for injuries in boxing, rugby football, association football, and karate.^{15,16,20} Foreign material may enter the eye in any sport. This seems to be the commonest cause of injury in the recently popularised jogging and aerobics, though excessive body movements in these activities have been responsible for self-induced body to eye contact. Introduction of foreign body material normally results in superficial mechanical damage. However, materials capable of producing toxic effects, such as lime from the line markings as illustrated in the study, may also be introduced, causing more severe effects. Injury by falling over is most likely to occur in sports where the participant is travelling at speed, for example skiing and horse riding.

Football has not previously been considered as a major cause of serious sport associated eye injury. This study, however, has shown that it is the commonest cause of sport associated eye injury in the west of Scotland. This is undoubtedly a function of the popularity of football in this area. In comparison a study from Ireland²⁰ showed hurling to be the most dangerous pastime. The football has previously been considered too large to enter the orbital aperture and therefore rarely to cause damage to the eye itself,² yet significant intraocular problems occurred in 49% of those injured with a football in this study.

Many injuries considered trivial or superficial may nevertheless progress to a more serious or long lasting effect, such as recurrent corneal erosion or ocular motility problems caused by periorbital bruising and adhesions. There is also a large group of more severe injuries, usually involving the anterior segment, resulting in hyphaema, traumatic uveitis, and/or angle recession. Long-term follow up is essential to determine the prognosis in these eyes. Extensive injury is not common, but retinal damage, optic nerve dysfunction, and disruption of the globe are all recorded in this study, each resulting in loss of acuity and of the affected eye in two cases.

Sport associated eye injuries are preventable.¹⁸ None of the injured patients in this study were noted to be wearing suitable eye protection (except two swimmers). Face and eye protection has been shown to be of value in hockey and squash^{18,19} and is available commercially. In tennis and badminton corrective glass spectacles do provide some pro-

tection,⁷ but it is now thought that during any sport plastic safety glasses should be worn (with or without correction). Skiers should always wear protection against ultraviolet light. Swimming goggles should be fixed to the face with a non-elastic strap to prevent them springing backwards into the eye.¹⁴

Devising suitable eye protection for use while playing football (rugby or association) is a more difficult problem, as by their very nature these games would require protective gear which would have to be firmly fixed to the head, and any suitable device may inadvertently injure other players or encourage the use of the head as a weapon. Furthermore, compelling players to wear any such protector would be impossible, as many youngsters participate in football on an unsupervised or informal basis.

Although these 246 cases represent only 1.1% of the total of 26 609 new patients seen in this combined casualty department over the 18-month study period, they represent a significant number of preventable injuries in a young population.

In summary, most sport associated eye injuries are relatively minor and can be treated on an outpatient basis. However, a significant number result in more serious damage which may threaten sight. This is an unacceptable price to pay in the pursuit of fitness and relaxation.

I would like to thank the Casualty Department nursing staff for their co-operation, and Miss Clare Doran for typing the manuscript.

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Iris atrophy with hypoperfusion and microneovascularisation

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SUMMARY A series of 17 patients with stromal atrophy, hypoperfusion, and microneovascularisation of the iris investigated in the Glaucoma Investigation and Research Unit are described, and their iris angiograms were compared with those of normal irides of patients in the same age group seen in general clinics. In all but one of the 17 cases this iris atrophy was associated with glaucoma or ocular hypertension, which appeared to be secondary to the iris changes. The condition was bilateral and presented a typical slit-lamp appearance, with subtle evidence of microneovascularisation. There was neither history nor clinical evidence of previous trauma, heterochromia, or intraocular inflammation. The commonest form of iris atrophy affected the inner third of the iris stroma in a patchy manner, often with sparing above. However, diffuse atrophy occurred in two cases, and there were two cases of 'senile tears' of the iris. Some accompanying atrophy of the pigment epithelium was usual but less prominent. The changes on fluorescein angiography of the iris included the late appearance of dye with a long arteriovenous circulation time, fewer arteries than normal with sectorial hypoperfusion, leakage of dye from the pupil margin and peripupillary neovascularisation, stromal tufts, and sometimes more complex stromal microneovascularisation. An expanded prominent lesser vascular circle was a common feature of the condition. The condition is bilateral and distinct from other forms of iris atrophy. In all cases the iris changes appeared to be secondary to the vascular hypoperfusion and were not consistently associated with evidence of gross vascular disease. All patients had grey (blue) irides, and this may be an aetiological factor. The condition appears common enough to form a significant group of glaucoma patients and to be a separate clinical entity.

The association of iris anomalies with glaucoma is well recognised. They are commonly seen with congenital and developmental glaucomas,¹ particularly in familial hypoplasia of the iris,² hypoplasia of the iris due to congenital rubella,³ aniridia,⁴ and in iridocorneal and irideal dysgenesis as seen in Rieger's syndrome and Peters' anomaly.^{5,6} In later life essential atrophy of the iris,^{7,8} Chandlers syndrome,⁹ and the iris naevus syndrome (ICE syndrome)¹⁰ form a group of cases distinct from the entity of iridoschisis.¹¹ Anterior segment pigment dispersal syn-

drome is associated with changes in the pigment epithelium of the iris, and a recent paper describes anomalies of the iris vasculature in this condition.¹² Changes in the iris are also present in pseudoexfoliation of the lens capsule associated with glaucoma¹³⁻¹⁵ and Fuchs' heterochromic cyclitis,^{16,17} and atrophy of the iris has long been recognised after acute angle closure glaucoma.¹⁸

We have recently observed a series of cases distinct from the foregoing which show stromal atrophy of the iris, iris hypoperfusion, and microneovascularisation. These cases are distinct enough to form a separate clinical entity. They are usually, but not invariably, associated with glaucoma. The purpose of this paper is to describe the findings in detail, consider their relationship to glaucoma, and to speculate on the aetiology of the observed changes.

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Materials and methods

A series of 17 patients with varying degrees of atrophy of the iris stroma were investigated at the Glaucoma Investigation and Research Unit of the Royal Victorian Eye and Ear Hospital. There were 10 males and seven females with ages ranging from 67 to 89 years (mean 78, SEM 2 years). In all cases the colour of the iris was grey (or blue). Eight patients had chronic open angle glaucoma, seven patients had varying degrees of ocular hypertension with open angles, one had subacute angle closure glaucoma but had not suffered an acute attack of glaucoma, while one patient was discovered to have iris atrophy with normal pressures. Six patients had started treatment for raised intraocular pressure with timolol maleate and pilocarpine hydrochloride only some months before the iris atrophy was noted.

All the patients were examined carefully, and the iris changes and any evidence of pigment epithelial loss were recorded. Contact specular microscopy was performed with the Pocklington contact specular microscope.

All the patients underwent fluorescein angiography of the iris to delineate the iris vascular changes in this condition. Fluorescein iris angiography was performed with a Nikon camera and 105 mm macro lens attached to the side of the Zeiss fundus angiography camera, utilising the light source and filter; this left the eyepiece of the angiogram camera free for use by an observer. The subjects received an intravenous bolus injection of 10 ml of 25% sodium fluorescein.

The time of first appearance of the dye (from its intravenous injection to its appearance in the iris vessels) and the arteriovenous circulation times (the time from when the arteries initially fill until the beginning of the venous phase) were measured, the number of radial arteries was estimated, and sectorial arterial filling defects were noted. Sectorial arterial defects were present when there was failure of a sector to perfuse during the first arterial phase of perfusion and filling occurred only some time after the venous flush had occurred elsewhere. A sectorial arterial defect was distinct from a delay in arterial perfusion; in the latter case the arterioles in a sector filled late in the arterial phase, or even very early in the venous phase. Leakage of dye from abnormal vessels was also recorded.

In view of the finding of iris hypoperfusion, intravenous digital subtraction angiography was performed on 10 patients to exclude internal carotid artery disease, which has been reported in ischaemic ocular inflammation.¹⁹ A non-ionic contrast medium, Iopamira 300 was used, and the catheter tip was placed in the right atrium. This enabled us to examine



Fig. 1 Well marked atrophy of the inner third of the iris stroma in a male aged 73 years with ocular hypertension. The atrophy does not affect the upper third of the iris stroma and lies almost entirely internal to an expanded lesser vascular circle of the iris.

the carotid bifurcation, aortic arch, intracerebral circulation to the level of the siphon, and the vertebral arteries.

For comparison the iris angiograms of a series of 10 patients, eight females and two males of similar age (range 69 to 85 years, mean 77, SEM 2 years) were examined. The iris appeared normal on slit-lamp examination in all these patients.

Results

The changes we describe were similar though not equal in degree in each eye of all patients. No patient suffered from diabetes mellitus and intraocular pressure was controlled to within the normal range at the time of angiography. All cases showed atrophy of the iris stroma, and this took several forms:

1. *Atrophy of the inner third of the iris stroma internal to the lesser vascular circle of the iris.* The lesser vascular circle of the iris then appeared to be expanded, so that in the affected areas it was a greater distance from the pupil margin than in normal subjects. The atrophy was irregular and patchy, often with sparing of the upper third of the iris stroma, so that the lesser vascular circle was also irregular in outline and closer to the pupil above. This form of iris atrophy was the most common type and was present in varying degrees in 14 cases (Figs. 1, 2). The appearance was distinct from the 'shredded wheat' appearance of iridoschisis, where fine strands of 'shredded' stroma float partly free in the anterior chamber.

2. *Diffuse atrophy of the iris stroma.* There was a generalised loss of the normal crypts and collarette with the appearance of an open, thin sponge-like structure through which the pigment epithelium was



Fig. 2 Marked atrophy of the iris stroma in a female aged 80 years with chronic open angle glaucoma. Below, the atrophy also involves the pigment epithelium of the iris so that there is a through-and-through defect. The upper third of the iris stroma is unaffected. See Fig. 5 for the pigment epithelial loss.

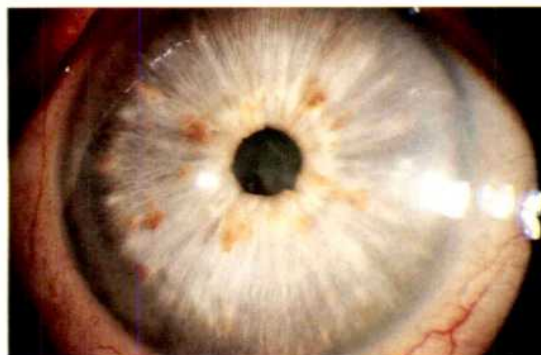


Fig. 4 'Senile tears' of the iris stroma in a female aged 83 years with chronic open angle glaucoma. These 'tears' have the appearance of multiple fine tears at the pupil margin due to small atrophic defects in the stroma. There is loss of the pigment ruff.

visible. Two cases showed this form of stromal atrophy (Fig. 3).

3. 'Senile tears' of the iris. This unusual finding was bilateral, with the appearance of multiple fine tears at the pupil margin; the iris stroma was particularly involved, but there was also loss of the collarette. There was neither a history nor signs of contusion injury in the anterior segment in these patients. 'Senile tears' were present in two cases (Fig. 4).

An accompanying atrophy of the pigment epithelium of the iris was usually less marked than the stromal atrophy, with the following features:

1. Loss of the pigmented ruff at the pupil margin; this was present in all cases to some degree (Fig. 4).

2. Diffuse atrophy of the pigment epithelium of the iris, so that there was diffuse light reflux through the pigment epithelium on retroillumination. This

was usually present in the inner third of the iris but was more widespread in the patients with diffuse stromal atrophy. This finding was present to some degree in all cases.

3. Gross patchy atrophy of the pigment epithelium in the region of, but less extensive than, the stromal atrophy in the inner third of the iris. This was present in three patients, who were not affected by herpes simplex or herpes zoster (Fig. 5).

4. Diffuse scatter of pigment granules through the iris stroma was seen in three patients.

On slit-lamp examination evidence of microneovascularisation of the iris was difficult to detect, but the following changes were noted: very fine vessels close to the pupil margin were seen in six patients; some radial vessels were seen in the atrophic inner third of the iris in five patients; microangiomas were

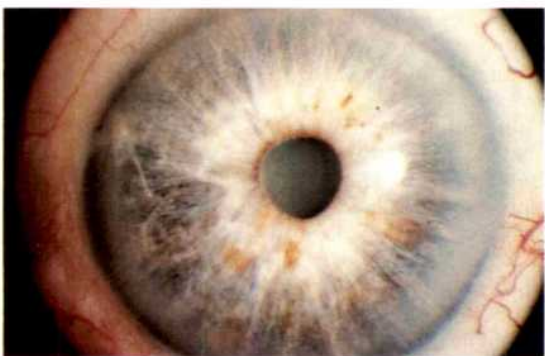


Fig. 3 Diffuse atrophy of the iris stroma so that the pigment epithelium may be seen through the interstices of the stroma in the outer half of the iris in a female aged 64 years with ocular hypertension.



Fig. 5 Gross patchy atrophy of the pigment epithelium of the iris shown on retroillumination of the iris in the same eye as Fig. 2. This patient had not suffered previous herpes simplex or zoster in either eye.

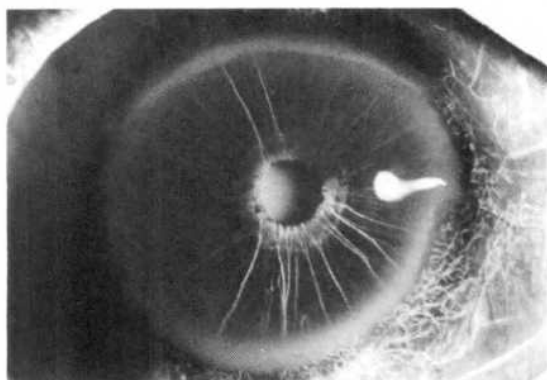


Fig. 6a Iris angiogram at 55 seconds in a male aged 84 years with diffuse iris atrophy and chronic open angle glaucoma. The very first dye appeared at 48 seconds. Marked segmental perfusion defects are still seen. There is early evidence of filling of the peripupillary plexus but there is still no venous filling. Nine definite arteries are demonstrated.

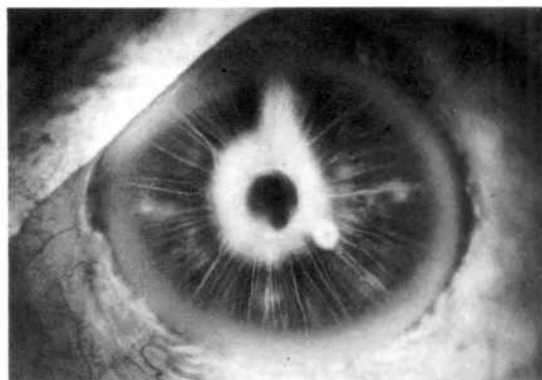


Fig. 6c At 96 seconds there is a smoke stack effect from the leaking peripupillary plexus.

present at the depigmented pupil margin in three patients.

Fluorescein angiography of the iris showed abnormalities in all patients. There was some difficulty in differentiating arterial from venous filling, but we noted a change in the number and density of vessels which we considered to be a change from arterial to venous perfusion. The findings were as follows:

1. The appearance of dye was delayed, sometimes markedly, in all patients, appearing at a mean of 26 (SEM 3) seconds, range 15 to 51 seconds (Fig. 6a).

2. There was a long arteriovenous circulation time and sometimes venous filling was extremely slow or very difficult to determine precisely: mean arteriovenous circulation time 11 (SEM 2) seconds, range 3 to 30 seconds (Fig. 6a).

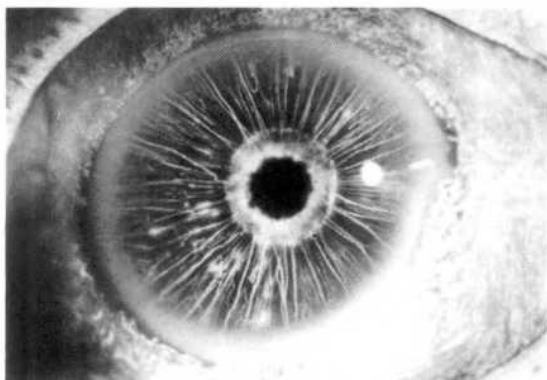


Fig. 6b At 76 seconds venous filling is established. There is a well marked peripupillary plexus which is leaking heavily and mid stromal leaking tufts are also seen.

3. Hypoperfusion of the iris was a feature of all cases with (a) a small number of arteries, always less than 30 (mean 17, SEM 1, range 10 to 28) (Figs. 6a, 7a); (b) the arteries were usually very thin and attenuated, though sometimes a few dilated radial vessels were present (Figs. 7a, 8a). The arterioles not infrequently appeared beaded (Fig. 9).

4. In 10 patients large sectors of iris appeared to be without arterial perfusion with late venous filling. In five of these almost half of the iris appeared to have very little arterial supply (Figs. 6a, 7a).

5. Leakage of dye from the pupil margin occurred in all cases and was often quite marked, with a smoke stack effect in late pictures due to upward circulation of the dye (Figs. 7b, 7c, 10, and 11).

6. Peripupillary neovascularisation was distinct from pupillary leakage and was present in 16 cases (Figs. 6c, 11). There was a fine dense plexus of

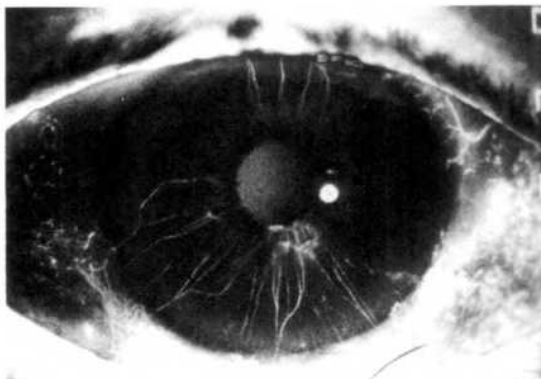


Fig. 7a Iris angiogram at 26 seconds of the same patient as Fig. 3 with diffuse iris atrophy and ocular hypertension. The first dye appeared at 22 seconds. At 26 seconds the venous phase is still not established. There are marked sectorial filling defects from 2 to 4 and 9 to 11 with thin attenuated arteries. Early leakage is occurring in the mid stroma.

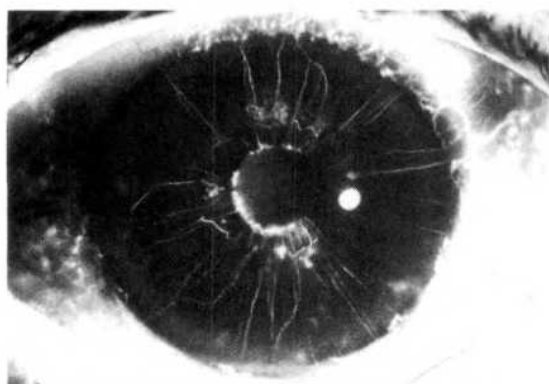


Fig. 7b At 33 seconds some sectorial defects in perfusion are still present. Complex neovascularisation is seen in the inner third of the stroma. Pupillary leakage is prominent.

leaking vessels adjacent to the pupil margin but not extending as far as the lesser vascular circle of the iris. The leakage was very heavy in some cases, again causing a smoke stack effect in the late pictures (Figs. 6b, 8b).

7. In addition, leaking tufts or vascular nodules occurred elsewhere in the stroma in eight patients. These were not usually numerous and were most common in the region of the lesser circle of the iris (Figs. 6b, 8b).

8. In six patients more extensive and complex neovascularisation was present elsewhere in the stroma with heavy leakage (Figs. 7b, 7c, 8b).

9. An expanded and prominent lesser vascular circle of the iris was present in nine patients. In these the iris atrophy affected the inner third of the iris, so that the lesser circle was much further from the pupil margin than normal. This prominent lesser circle did

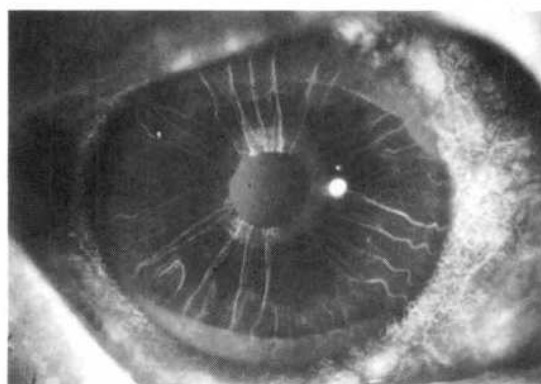


Fig. 8a Iris angiogram of a female aged 78 years with atrophy of the inner third of the stroma and ocular hypertension. The first dye appeared at 17 seconds. At 20 seconds there is arterial perfusion of thin attenuated arteries. There is very early filling of the peripupillary plexus. Vessels of the expanded lesser circle are starting to fill.

not leak, suggesting that it was due to dilatation of pre-existing anastomoses and filled before the venous flush, after the initial arterial filling. Iris atrophy was often not present in the upper third of the iris, and then the lesser circle was at the normal distance from the pupil margin. The arterial perfusion of the iris was usually much better in the upper third in such cases (Figs. 8b, 11).

10. Peripheral vascular loops were present and prominent in eight patients. These did not reach the inner iris and appeared as loops which perfused early, did not leak and were not associated with venous drainage (Fig. 9).

11. Arterial beading was present in six cases (Fig. 9).

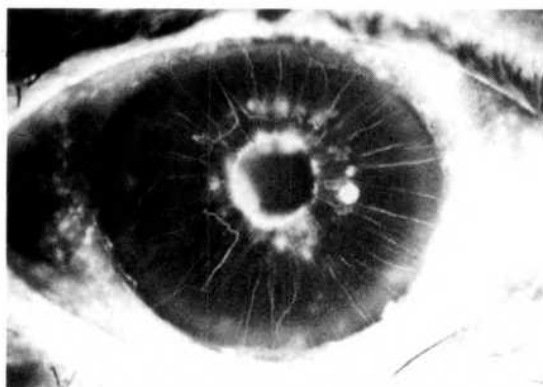


Fig. 7c At 50 seconds all sectors of the iris are filling in the venous phase. There is heavy peripupillary leakage from complex new vessels in the inner third of the iris stroma with commencing smoke stack effect.

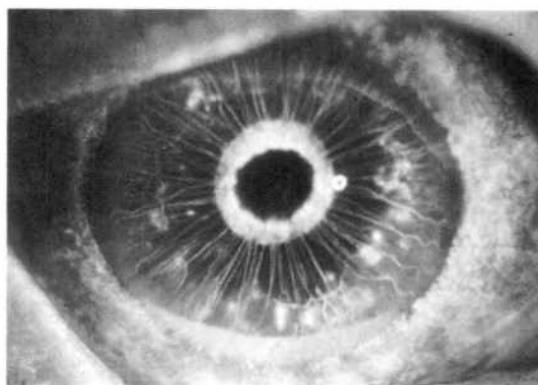


Fig. 8b At 37 seconds, in the venous phase, numerous tufts are seen in the region of the lesser vascular circle of the iris. There is considerable leak from the peripupillary venous plexus.

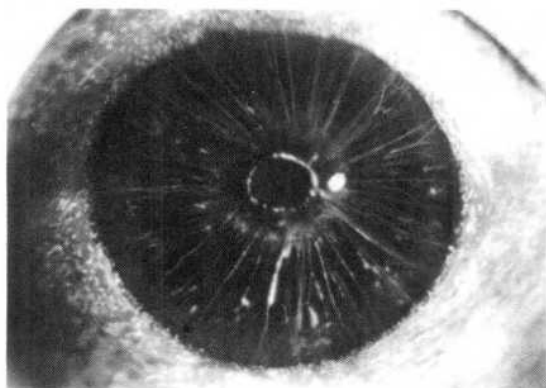


Fig. 9 Iris angiogram of a male aged 83 years with 'senile tears' of the iris and ocular hypertension. At 34 seconds there are prominent peripheral loops with beading of the vessels.

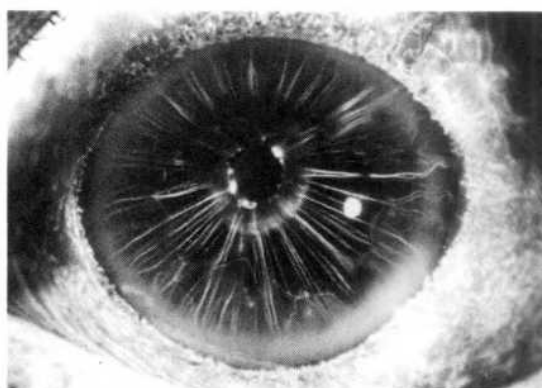


Fig. 11 Iris angiogram in same eye as Fig. 1. The first dye appeared at 20 seconds. At 35 seconds (venous phase) an expanded lesser vascular circle is well shown with peripupillary leakage of dye.

The neovascular changes were related to the iris atrophy in the following ways: The expanded lesser circle was related to the commonly occurring atrophy of the inner third of the iris. Although segmental hypoperfusion of the iris did not appear to be closely related to segmental atrophy of the iris, atrophy was uncommon superiorly and arterial perfusion was usually best in this area. In some cases where iris atrophy was particularly marked there was a heavy leakage of dye in the area of the atrophy, probably from damaged, compromised, or exposed radial vessels in the area.

There was a relationship between the iris changes and raised intraocular pressure. Most of these patients presented for investigation of raised intraocular pressure. Eight patients were under treatment for chronic open angle glaucoma with raised intraocular pressure. Seven patients were seen with

elevated intraocular pressures in the absence of both pathological cupping of the optic disc and of field loss. One patient was seen with typical subacute angle closure glaucoma but had not developed an acute attack. In this patient the iris atrophy was not typical of acute glaucoma but rather of the condition which we are describing. In one eye there was no rise in intraocular pressure, and this is the only case which we have seen with the findings typical of the condition in the absence of raised intraocular pressure.

On gonioscopy all angles were wide and open all round except for the case of subacute angle closure glaucoma. In most patients trabecular pigmentation was recorded as moderate, but in three it was light and in two heavy. The iris processes were scanty in all but two cases, in which the iris processes were fine, moderate in number, and extended to the trabecular meshwork. The slit-lamp evidence of microneovascularisation was very subtle, and no fine vascular changes were noted in the angle on gonioscopy.

Specular microscopy showed a significant decrease in endothelial cell counts in the patients with iris atrophy compared with age matched normal controls (mean 2202, SEM 63/mm² in iris atrophy; mean 2887, SEM 90/mm² in the controls; $p < 0.01$ Wilcoxon matched-pairs signed-rank test). There was an increase in pleomorphism and polymegathism of the endothelial cells in the patients with iris atrophy.

Arterial hypertension requiring medication was present in four patients and ischaemic heart disease requiring medication was present in two. The remainder were in good general health, and neither diabetes mellitus nor chronic respiratory disease was present in any of the patients.

Digital subtraction angiography showed no significant abnormality in six cases with abnormalities in

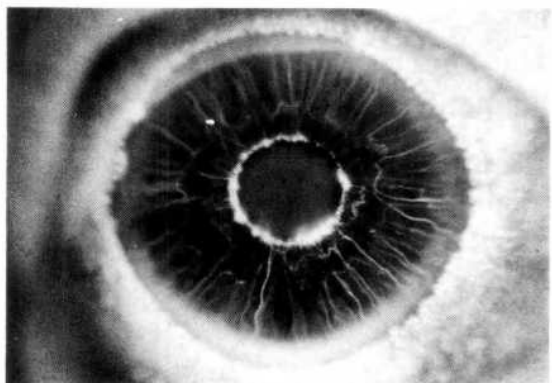


Fig. 10 Iris angiogram in female aged 86 years with atrophy of the inner third of the iris and chronic open angle glaucoma. The first dye appeared at 20 seconds. At 40 seconds there is well marked pupillary leak and well developed lesser circle of the iris. The pupillary leak is showing a smoke stack effect.

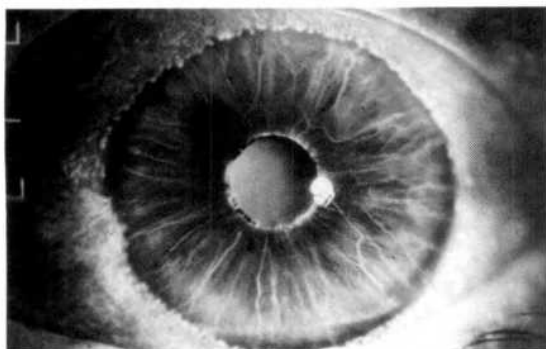


Fig. 12a Iris angiogram in female aged 74 years with normal grey iris. The first dye appeared at 21 seconds. At 48 seconds there is good perfusion of the iris, slight pupillary leak only and no other evidence of microneovascularisation nor expanded lesser circle.

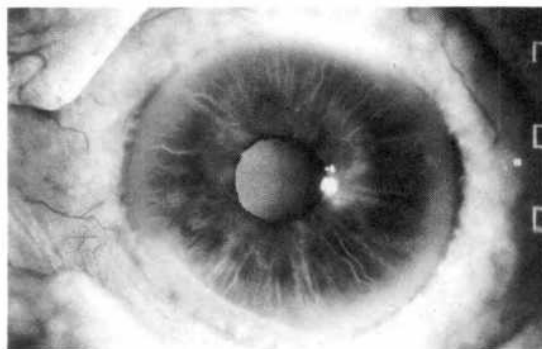


Fig. 13 Iris angiogram in female aged 85 years with normal grey iris. The first dye appeared at 18 seconds. Late picture at 121 seconds showing no significant leakage of dye. Note the clarity of the pupillary ruff.

four cases. There was 50% to 60% stenosis of the origins of both internal carotid arteries in the 83-year-old male with 'senile tears' of the iris and ocular hypertension. A 50% stenosis of the right internal carotid artery origin, with a lesser narrowing of the external carotid origin and a haemodynamically insignificant plaque at the origin of the left internal carotid artery, was present in the 85-year-old female with atrophy of the inner third of the iris and chronic open angle glaucoma. In this patient the iris atrophy was less on the side of the significant carotid stenosis. In the male aged 73 years, with atrophy of the inner third of the iris and ocular hypertension, there was a mild but insignificant narrowing of the origin of the right internal carotid artery, and once again the iris atrophy was more marked on the contralateral side with no stenosis. Finally, in the male aged 75 years with diffuse bilateral iris atrophy and chronic open angle glaucoma there was a very slight irregularity at, and just distal to, the origin of the right internal carotid artery, but no disease was demonstrated in the left carotid system.

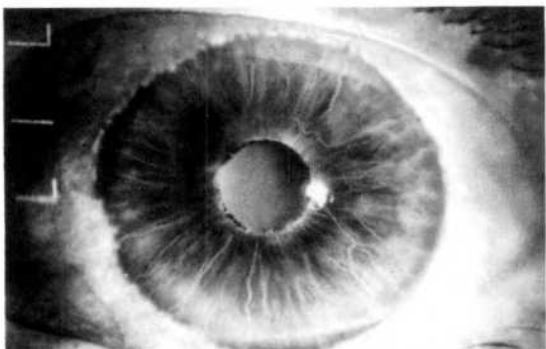


Fig. 12b At 96 seconds perfusion is fading and there is still no significant leakage. The pupillary ruff is well seen.

On fluorescein angiography of the normal group the mean arterial time was mean 20 (SEM 2) seconds, range 14 to 27 seconds. The eyes were well perfused with a normal number of radial arterioles of good calibre, though a small area of sectorial hypoperfusion was present in one patient. Six patients showed some pupillary leak, though this was slight except in one patient where it was moderate. No patient showed peripupillary neovascularisation nor expanded lesser circle. One patient showed one leaking tuft. There was no arterial beading and no neovascular plexuses had developed (Figs. 12a, 12b, 13).

Discussion

This group of patients is distinct enough to form a clinical entity. The atrophy of the iris stroma was bilateral and most commonly patchy affecting the inner third of the lower iris stroma, though diffuse atrophy and an appearance of local notching of the pupil margin were also seen. Although the stromal atrophy of the iris varied in its appearance, the vascular changes found on fluorescein angiography of the iris were similar throughout the group. There was evidence of hypoperfusion of the iris and microneovascularisation. The arterial hypoperfusion of the iris was striking in degree, being much more marked than age related changes, and we believe that it is the cause of the iris changes, rather than occurring secondarily to the atrophy of the iris. In particular, hypoperfusion was usually less marked above and the iris atrophic changes were also less frequent here. Sectorial defects in hypoperfusion, distinct from physiological delay in filling described by Hayreh and Scott,²⁰ together with a delayed arteriovenous circulation time also support hypoperfusion as the cause of iris atrophy.

It is possible that the vascular changes are secondary to a rise in intraocular pressure, but we have seen the condition in the absence of raised intraocular pressure. In some cases with less atrophy of the iris the ocular hypertension was relatively mild, suggesting a progressive process which may go on to a more extreme rise in intraocular pressure as the process advances. Thus the ocular hypertension appears to be secondary to the iris changes. Further, six patients had received no previous treatment for their ocular hypertension, so it is unlikely that the vascular changes were secondary to glaucoma medication.

The iris microneovascularisation was a subtle change which had previously been noted among the vascular changes in anterior segment pigment dispersal syndrome, which was thought to be due to a congenital mesodermal defect.¹² This iris microneovascularisation was much less marked than the gross neovascularisation of the iris which occurs in neovascular glaucoma following previous central retinal vein occlusion, but its pathogenesis may be similar, though in the cases we describe the iris atrophy arose as a result of more gradual and more localised ischaemia than in central retinal vein occlusion. Clinically, the iris microneovascularisation is difficult to detect, but fine vessels may be seen close to the pupil margin, from which the pupillary ruff is usually lost, as in the loss of pupillary ruff previously reported in pseudoexfoliation of the lens capsule.^{13,14} Fine radial vessels may also be seen with the slit-lamp high power, but these are probably normal radial vessels which do not leak. The microangiomas are similar to the vascular tufts at the pupil margin described by Cobb.²¹

The pupillary leakage of dye which was seen in all cases was probably due to neovascular tufts occurring at the pupil margin and was much more marked than that seen in some elderly patients. The heavy pupillary leakage from fine vessels may be either from fine neovascularisation or from damaged vessels of the capillary plexus which is normally present in this location. The sphincter muscle, which is supplied by the capillary plexus, remained intact. The expanded prominent lesser circle of the iris appeared to be formed by opening up of a pre-existing arterial anastomosis, and this became displaced outwards with loss of the inner third of the stroma. The leaking tufts in the iris stroma may be consistent with early neovascularisation, ultimately developing into the more complex systems of neovascularisation sometimes seen in the stroma on angiography. The beading of the arterioles is consistent with changes occurring as a result of damage to the vessel walls.

The most typical atrophy of the iris stroma affected the inner third of the stroma, often being patchy in distribution, with sparing above. This was accom-

panied by some loss of the pigment epithelium and is consistent with this inner part of the iris being more susceptible to the effects of hypoperfusion occurring in later life. Anterior segment pigment dispersal syndrome is also associated with a relative hypoperfusion of the iris but this is probably present from birth, with some degree of hypoplasia of the iris stroma. This results in an instability of the pigment epithelium which is easily shed in a patchy manner in the region of the dilator muscle in susceptible individuals.

Patients in the current series were elderly, and, although some were under treatment for arterial hypertension or ischaemic heart disease, most were in good general health for their age, with no chronic respiratory disease or other cause of peripheral hypoxia which might predispose to pupillary leakage²² or other changes. Although carotid obstruction has been reported in ischaemic ocular inflammation,¹⁹ digital subtraction angiography failed to show a significant abnormality in most patients, excluding subclinical carotid insufficiency with hypoperfusion of the head and neck as a major aetiological factor in this condition.

The relationship of the iris atrophy in this series to glaucoma may be partly due to pigment release, most of the angles showing marked or moderate pigmentation of the trabecular meshwork. Iris processes were not a prominent feature of this condition, as they often are in various forms of iris hypoplasia and anterior segment pigment dispersal syndrome.²³ However, the hypoperfusion which causes the iris atrophy may also affect the trabecular mesh, causing ischaemic changes which result in an increased resistance to aqueous outflow. The less marked degree of iris atrophy often seen in chronic open angle glaucoma suggests that this may be a common mechanism in the production of increased resistance to aqueous outflow. The more permeable iris capillaries may also affect aqueous dynamics by allowing leakage of plasma components into the aqueous.

Diffuse atrophy of the iris stroma occurred less commonly than atrophy of the inner third of the stroma, but was accompanied by similar vascular changes and ocular hypertension. Diffuse reflux of light through the pigment epithelium was also a feature of these cases.

'Senile tears' of the iris gave an appearance of tears at the pupil margin but were bilateral, with no other suggestion of contusion injury. They appear to be due to local atrophy of the iris stroma close to the pupil. Hypoperfusion of the iris was present in these cases with prominent microneovascular changes and segmental hypoperfusion; this hypoperfusion may be a factor in producing this local stromal change.

The changes in iris stroma which we have described

were much more marked than any senile changes which we have previously observed and constitute a distinct disease entity. Although the changes were expressed in several different ways, which we have described, the underlying vascular changes were essentially similar in all, and much more marked than senile vascular changes. The findings in the comparable group of elderly patients with normal irides which are described here demonstrate that, although some slight changes in perfusion and a little pupillary leakage may occur in otherwise normal elderly patients, they are only minor in degree, and the abnormal changes which we have described are pathological in nature.

Kottow²² has remarked that although some vascular abnormality may be seen on fluorescein angiography in elderly patients it is difficult to be sure whether even these mild changes are really age related or pathological. The vascular changes were different from the progressive midstromal changes we have observed in cyclitis²⁴ and usually much less florid than the changes previously described in pseudoexfoliation of the lens capsule.¹⁵

The bilaterality of the changes suggests that the iris atrophy is an abiotrophy appearing in later life, associated with endothelial cell changes. These changes are not as marked as those in Fuchs' endothelial dystrophy, which Bahn *et al.*²⁵ have considered to be due to an endothelial dystrophy. The vascular hypoperfusion common to all cases suggests that this is the causal mechanism, but why these small arteries should fail in later life is not clear. This condition does not appear to be part of a generalised vascular disease but rather is a local defect in the arterial circulation of the iris. Iridoschisis and some forms of the ICE syndrome are other iris conditions which also present later in life, but they are quite different in appearance from the entity which we describe.

There were seven patients with ocular hypertension only, without cupping of the optic discs. The absence of optic disc damage in the presence of hypoperfusion of the iris suggests that there is no associated hypoperfusion of the posterior segment of the eye, which if present would render the optic disc more susceptible to the effects of ocular hypertension.

It is striking that all patients had grey (or blue) irides. Although hypothetical, this suggests that these irides are far more susceptible to the effects of this hypoperfusion. A further factor in the development of atrophy may be a greater susceptibility of light coloured irides to the effects of solar radiation. The higher incidence of iris atrophy in males in this series may relate to their increased exposure to such solar radiation. The sparing of the upper third of the iris stroma which is usually shielded by the upper lid

also suggests that exposure is a factor in the aetiology of this condition.

In conclusion, atrophy of the iris due to hypoperfusion with microneovascularisation as we have described is a distinct clinical entity, occurring moderately frequently in the elderly. It is a local condition of the iris and may be diagnosed on slit-lamp examination, with confirmation of hypoperfusion by fluorescein iris angiography. It is commonly, but not invariably, associated with glaucoma.

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A 6½-years survey of intraocular and intraorbital foreign bodies in the North-west Frontier Province, Pakistan

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SUMMARY A survey of 198 patients (210 eyes) with intraocular or intraorbital foreign bodies is presented. Most were males between 16 and 30 years of age, and 6.1% of cases were bilateral. The commonest cause was a flying particle while using a hand hammer, followed by fragments of bomb and mine blasts. Intraorbital foreign bodies occurred in 78 eyes and intraocular foreign bodies in 132 eyes. Irreparable damage caused 13 eyes (6.2%) to be enucleated. Ten eyes developed severe endophthalmitis or panophthalmitis requiring evisceration. One hundred and thirty-four (63.8%) foreign bodies were removed, and 76 (36.2%) foreign bodies could not be removed. The causes of non-removal, the various complications, and the pattern of foreign bodies in the eye or orbit in Pakistan are discussed and compared with those of other regions.

Foreign bodies of the eye or orbit account for a small but significant part of ocular trauma. The significance of this type of injury is heightened by its association with occupation and the serious complications it causes both early and late. It was while studying ocular trauma in general at the Khyber Teaching Hospital, University of Peshawar, Pakistan, from January 1978 to August 1984 that we took a deeper look at the local pattern of intraocular and intraorbital foreign bodies, their distribution, causes, and complications. Two cases of deep corneal foreign bodies seen are excluded from this study.

Material and methods

Case records were derived from the files of the Khyber Teaching Hospital. A specific history about the type of object and occupation at the time of injury was taken from all patients. An examination was then carried out with a slit-lamp and direct and indirect ophthalmoscopes, when possible. In severe cases with much oedema of the eyelids the examination was carried out under general anaesthesia with an indirect ophthalmoscope and operating microscope.

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X-ray of the orbit, with antero-posterior and lateral views, plain, and with a limbal ring or contact lens with radio-opaque dots was carried out. Final localisation was done with a Roper-Hall foreign-body locator. In cases with magnetic foreign bodies a magnet with an anterior or pars plana approach was used. Non-magnetic foreign bodies were removed mainly with microforceps from the anterior chamber or iris, and by lens extraction when situated in the lens. Posterior segment non-magnetic foreign bodies could usually not be removed owing to lack of facilities for vitrectomy.

Separate removal of the foreign body was not attempted in eyes with gross infection or irreparable damage. In such cases evisceration or enucleation was done as a primary procedure. Follow-up was erratic, but it is presumed that at least patients with complications presented again. At follow-up the eyes was again examined and the observations recorded.

Results

Out of 1971 patients (2060 eyes) who sustained ocular injuries severe enough to require admission, foreign bodies in the eye or orbit were found in 198 patients (210 eyes, or 10.2%), of whom 28 were Afghan refugees. 195 patients (98.5%) were male, (1.5%)

female. Most of the patients (89%) fell in the age group 16-30 years (Table 1). 6.1% of the injuries were bilateral, of which two-thirds occurred in Afghan refugees. Intra-orbital foreign bodies were present in 78 eyes (37%) and intraocular foreign bodies in 132 eyes (63%). The commonest object was a flying iron particle while the patient was using a hand hammer (53.3%). This occurred entirely among patients working in motor vehicle repair shops or factories manually manufacturing weapons at Dara Adam Khel. These injuries accounted for the majority of magnetic foreign bodies. They were followed in frequency by injuries caused by fragments from bomb and dynamite blasts (20.5%) and bullets from firearms or pellets from airguns. Foreign bodies from fireworks caused bilateral multiple corneal and anterior chamber injuries in three patients (2.9% eyes). Injuries from pieces of wood while chopping occurred in 2.9% eyes, while one patient had a large piece of glass in the orbit following a road traffic accident (Table 2). This patient had a blow-out fracture and vertical squint and required multiple operations.

The foreign body was removed from the eye or orbit in 63.8% eyes, while in 36.2% of cases removal was not possible (Table 3). This was due to double penetration, with the foreign body lying posteriorly in the orbit, or to non-magnetic foreign bodies in the posterior segment, or because the patient presented very late and the foreign body was perhaps encapsulated in a tough fibrous capsule. Some of these last patients presented with siderosis bulbi.

Patients either presented within 24 hours of injury or 7-10 days later, when infections or early lenticular opacities had set in, or in a few cases even 1-2 months later with a healed perforations and cataract or secondary glaucoma. The average delay was five days. Small flying iron particles were responsible for the longer delays.

The common immediate complications (Table 4) were haemorrhage in the anterior chamber (4.8%) or vitreous (4.8%) and irreparable damage to the eye (4.3%) caused by large foreign bodies like bullets, airgun pellets, and fragments driven in by bomb or dynamite blasts. Other early complications were traumatic cataracts (5.2%) and gross infection (4.8%) in patients with delayed presentation. Complications seen in patients presenting very late or coming for subsequent follow-up were: traumatic cataract (9.0%), secondary glaucoma (5.7%), phthisis bulbi (5.2%), retinal detachment (3.8%), and siderosis bulbi (1.4%).

Discussion

Foreign bodies accounted for 10.2% of all ocular

Table 1 Age and sex distribution

Age group	No of patients	%*	Male	Female
0-15	18	9.09	16	2
16-30	166	88.84	166	0
Over 30	14	7.07	13	1
Total	198	100.00	195	3

*The percentage is of total number of cases with foreign bodies.

Table 2 Aetiological distribution

Causes	Number of eyes	%
Flying iron particles using hand hammer	112	53.3
Bomb and dynamite blasts	43	20.5
Firework injuries	6	2.9
Firearm injuries	22	10.5
Airgun pellets	20	9.5
Wood	6	2.9
Glass	1	0.4
Total	210	100.0

Table 3 Causes of non-removal

Causes	No.
Bomb fragments in orbit	22
Foreign body embedded in the angle	2
Orbital pellets	18
Failed removal of non-magnetic foreign bodies	15
Orbital bullets	9
Left hospital against medical advice	4
Failed removal of magnetic foreign bodies	3
Missed foreign bodies, now siderosis bulbi	3

Table 4 Complications of intraocular or intraorbital foreign bodies

Type of complication	No. of eyes	%
<i>Immediate</i>		
Irreparable damage	9	4.3
Vitreous haemorrhage	10	4.8
Hyphaema	10	4.8
Commotio retinae	1	0.5
Complete external ophthalmoplegia	1	0.5
Squint due to fixation of inferior rectus by foreign body	1	0.5
<i>Early</i>		
Traumatic cataract	11	5.2
Intraocular infection	10	4.8
Retained foreign body	76	36.3
Orbital cellulitis	1	0.5
<i>Late</i>		
Traumatic cataract	95	45.2
Secondary glaucoma	12	5.7
Phthisis	11	5.2
Retinal detachment	8	3.8
Siderosis bulbi	3	1.4

injuries during the same period (Khan MD, *et al.*, unpublished). The incidence in this study was about three per month, this appears to be somewhat higher than reported from the UK (two per month) in 1972,¹ Ceylon in 1964 (6.4%),² and Ireland in 1980 (8.4%),³ but lower than reported from India (28%)⁴ in 1985. However, when we consider that this study is composed of both intraocular and intraorbital foreign bodies, the incidence becomes almost similar to those from UK and Ireland. In sharp contrast to these observations are those in a study from Malawi,⁵ where not a single case of intraocular or intraorbital foreign body was reported.

Our figures are indicative of a crude, largely manual, or semiautomated industry, with a complete lack of protection at work, combined with an aggressive and criminally negligent attitude of the average person, whether young or old. This is shown by the large number of injuries from bullets and airgun pellets (20%). The almost exclusively male preponderance is similar to that reported elsewhere,^{1,6} and points towards the largely occupational nature of these injuries.

In our study flying particles account for 53.3% of injured eyes (56.6% of patients), compared with 63% reported by Percival¹ from the UK. Bomb blast injuries accounted for almost 20% of injured eyes and occurred mainly among victims of the war across the border. Firearm injuries occurred mainly during local scuffles, only two cases being in refugees. Percival,¹ on the other hand, reported only two cases of explosions and eight cases of shotgun pellets in 245 patients, while not a single case was reported from Ceylon² or Malawi.⁵

Airgun pellets deserve special mention. In this study they occurred in 9.5% of patients compared with 2.4% reported by Percival¹ and a similarly low number by Brinton *et al.*⁷ The ages of these patients ranged from between a few months to 56 years. The main cause of the injuries was the unsupervised use of potentially dangerous weapons by careless and ignorant youngsters. We also noticed an increase in the number of these injuries at festival times. A similar finding has been reported by Kreshon.⁸

Dynamite blasts accounted for 3% out of the 21% of blast injuries. They were found mainly to affect those working at the construction of roads in hilly areas, where dynamite is used for blasting rocks. This figure is much less than reported from India,⁹ where blast injuries affected roughly 9.3% of patients with intraocular foreign bodies.

There was a mild intraocular inflammation in all but 7.8% of eyes; these latter 7.8% represent 3% of eyes which required primary enucleation and 4.8% eyes which were grossly infected and subsequently required evisceration. Primary enucleation was done

only in those eyes which were damaged beyond repair. These figures are somewhat higher than reported by Percival.¹

Removal of the foreign body was not possible in 36% cases. They were mainly cases of intraorbital or posterior segment foreign bodies which could not be removed by forceps alone, as vitrectomy was necessary, for which we did not possess the required equipment. The major late complication was a gradually progressive lenticular opacity. In these cases extraction was done, but the visual outcome was poor in uniocular cases as we could not provide the majority of patients with either an intraocular implant or a contact lens. Secondary glaucoma occurred as frequently as reported by Percival.¹⁰ Most of these patients presented late, when little could be done for them. Pthisis bulbi, detachments, and siderosis bulbi occurred less frequently than reported by Percival.¹⁰ One reason could be the irregular and often infrequent follow-up, and many patients may have suffered in silence. The lack of a vitrectomy equipment proved to be a great handicap, for in many of these eyes vision might have been saved or at least improved if timely vitrectomies had been performed.^{6,7,11}

When going through the above figures the reader must bear in mind that they are much biased by the inclusion of the Afghan refugees. Afghan refugee patients made up only 11% of patients with injured eyes but accounted for 17% of intraocular or intraorbital foreign bodies. Afghan refugees accounted for 66.6% of bilateral foreign bodies. These patients are mainly the victims of bomb or dynamite blast injuries (Khan MD, *et al.*, unpublished), from which the morbidity is high.

Sympathetic ophthalmia was not seen in a single case in this study.

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Correspondence

Persistent choroidal detachment

SIR, Idiopathic uveal effusion syndrome (IUES) is characterised by serous detachment of the peripheral uvea in healthy, middle aged individuals frequently with associated bullous, non-rhegmatogenous retinal detachment. Intraocular surgery is a more common cause of choroidal detachment. We report the persistence of choroidal detachment after cataract extraction in a patient with documented IUES.

Case report

A 63-year-old black man with minimal background diabetic retinopathy (BDR) OS presented to the North Central Bronx Hospital eye clinic in November 1979 with a complaint of decreased visual acuity for two months. Examination was significant for corrected visual acuity of 20/20 OD and 20/100 OS with a spectacle correction of +2.25 sphere OD and +2.50 sphere OS. The left vitreous had a mild cellular reaction. The left fundus was characterised by a bullous, non-rhegmatogenous retinal detachment with an associated choroidal effusion (Fig. 1). Fluorescein angiography OS revealed retinal pigment epithelial changes, mild optic disc oedema, and mild BDR with macular oedema. There was late staining of the bullous retinal elevation. Ultrasonography OS disclosed vitreous band formation, a choroidal detachment, a possible retinal detachment, and thickening of the choroidal layer. No intraocular or retrobulbar mass was identified, and a diagnosis of IUES was

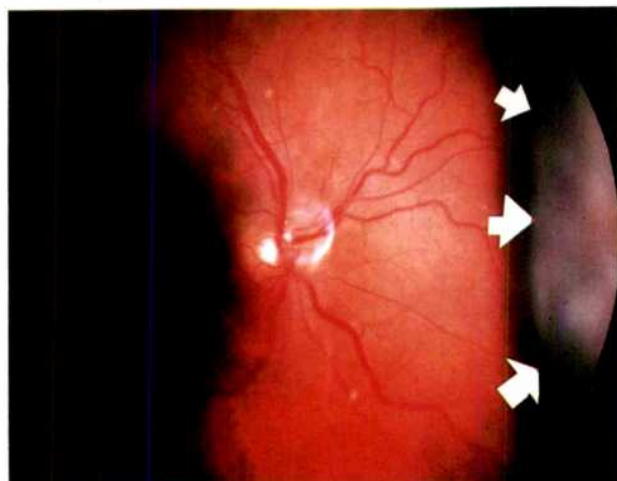


Fig. 2 Persistent postcataract extraction choroidal effusion (see arrows) OD.

made. The exudative detachment persisted OS and did not improve with subtenon methyl prednisolone (Depo-Medrol) 40 mg administered one month after presentation. A gradual spontaneous reduction in the bullous detachment was observed, with complete resolution of IUES over one year without additional therapy.

No further effusion was noted, but progressive posterior subcapsular cataractous changes occurred OU over the following five years. Extracapsular cataract extraction with a posterior chamber pseudophakos was performed OD five years after the spontaneous resolution of IUES in the contralateral (OS) eye. On the ninth postoperative day the patient developed a 360° postoperative choroidal detachment OD without evidence of hypotony or wound leak. The choroidal detachment persisted (Fig. 2), and five months postoperatively B ultrasonography confirmed the persistent 360° choroidal elevation (Fig. 3).

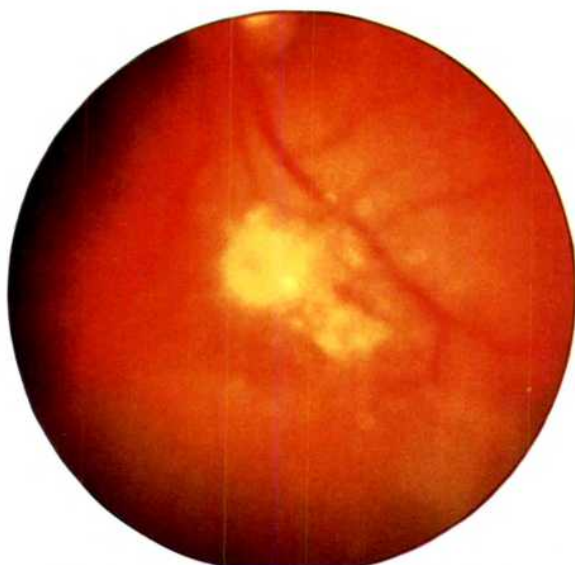


Fig. 1 Inferior retinal detachment with an associated choroidal effusion and intraretinal exudate; also note background diabetic retinopathy.

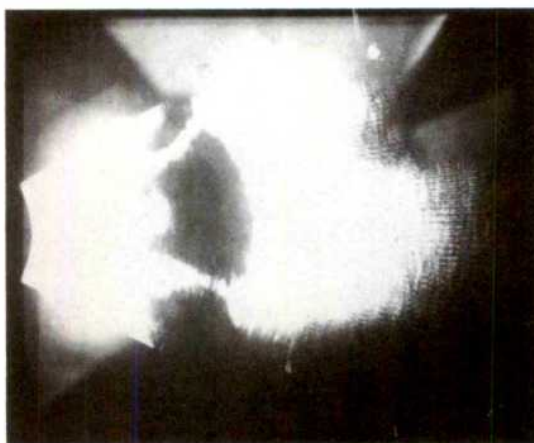


Fig. 3 B scan ultrasonography demonstrating 360° persistent postcataract extraction choroidal effusion OD.

Cataractous changes OS progressed, and extracapsular cataract extraction was performed nine months after cataract extraction OD. The postoperative course was uncomplicated OS despite the previously documented history of IUES. The postoperative choroidal detachment OD has persisted for a total of nine months.

Discussion

The persistence of choroidal detachment after cataract extraction five years after spontaneous resolution of contralateral IUES raises several issues relevant to the pathogenesis of these entities. The unusual persistence of a postoperative choroidal detachment OD supports the possibility of predisposing anatomical factors in the development of uveal effusion. Brockhurst¹ classifies uveal effusions as inflammatory, hydrodynamic, and idiopathic. Post-surgical hypotony and/or inflammation may precipitate uveal effusion in anatomically predisposed eyes. Such anatomical features have an apparent role in development of uveal effusion in patients with nanophthalmos.¹ Surgical inflammation and hypotony may precipitate persistent uveal effusions in nanophthalmic eyes with a known anatomical abnormality. Gass² suggests that IUES eyes are also predisposed because of a congenitally thickened sclera. A thickened sclera apparently predisposes the eye to vortex vein obstruction and more importantly acts as an abnormal

barrier to the transport of protein out of the eye by way of the uveoscleral pathway. These important underlying anatomical abnormalities have formed the basis for surgical attempts to cure IUES³ and nanophthalmic uveal effusions.¹

While nanophthalmic eyes have been proved to have thickened sclera,⁴ not all IUES sclera have been demonstrated to be thickened.² Our patient was not nanophthalmic, and no other predisposing factors were apparent. It seems obvious that there was a predisposition to effusion in this case, but its nature remains obscure.

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Obituary

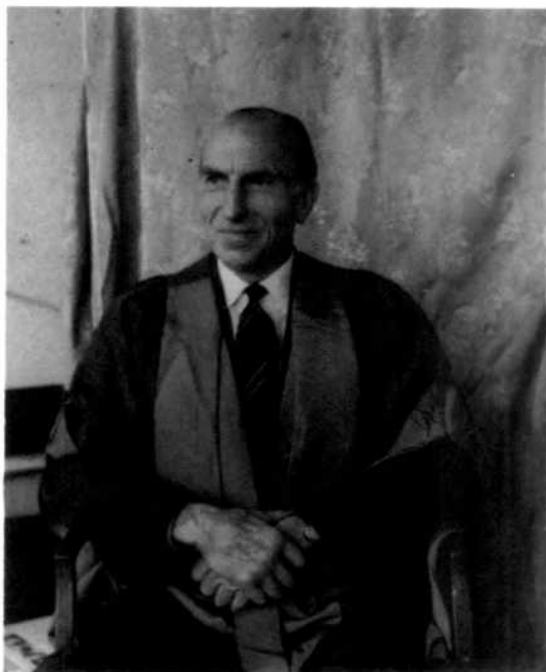
T Keith Lyle, CBE, MA, MD, M Chir, FRCP, FRCS

Thomas Keith Lyle died on 9 May at the age of 83. He was the son of Herbert Willoughby Lyle, MD, FRCS, who was an ophthalmic surgeon at King's College Hospital and at one time dean of the Medical School. Educated at Dulwich College and Sidney Sussex College, Cambridge, where he was an exhibitioner, Keith Lyle undertook his medical training at King's College Hospital, where he was an outstanding undergraduate, winning the Todd medal for clinical medicine.

He was in some doubt as to which branch of medicine he wished to follow and considered neurology as a possible choice but settled eventually for ophthalmology, receiving his early training at the Royal Westminster Ophthalmic Hospital. He was appointed to the consultant staff of the Royal Westminster Ophthalmic Hospital and of the National Hospital, Queen Square, in 1936 and to the consultant staff of King's College Hospital in 1938.

His career was interrupted by the outbreak of war, and as he had been made a civil consultant in ophthalmology to the RAF in 1934 he found himself in uniform immediately at the outbreak and served until the close of hostilities, during which time he was mentioned in dispatches. He reached the rank of temporary air commodore.

Keith Lyle took an early interest in the Faculty of Ophthalmology and became its president in 1968. He was



also a keen member of the Court of Assistants of the Society of Apothecaries and became master in 1962-3. He was appointed deputy hospitaller in 1960 and hospitaller in 1969 of the Most Venerable Order of the Hospital of St John of Jerusalem, a post he held until 1980, when he was honoured by the distinction of a Knight Grand Cross.

His abiding interest in ophthalmology was in ocular motility, and he became an international figure and world authority on the surgical aspect of this subspeciality. He was appointed president of the International Strabismological Association.

Many honours came his way. He gave the Doyné memorial lecture at Oxford in 1953 and the Alexander Welch lecture in Edinburgh in 1965. He gained the Nettleship medal in 1959 and the Richardson Cross medal in 1962.

He wrote several textbooks, the first of which was *Practical orthoptics in the treatment of squints* in 1937 with Sylvia Jackson; this was later rewritten with the help of K C Wybar. He also re-edited Chavasse's edition of *Worth's squints* with the help of the Hon G J O Bridgeman, and with A G Cross he edited *May and Worth's disease of the eye*, 13th edition. He made many contributions to textbooks of surgery by chapters on his subject.

Keith Lyle was a keen teacher and enjoyed instruction of students, both junior and senior. It was his interest in teaching which induced him to accept the burden of being dean of the Institute of Ophthalmology at a time when many Commonwealth students came to London to sit for the Diploma in Ophthalmology granted by the Royal Colleges. He was a man of great industry and was able to accept more than the average share of extramural duties because of the self-disciplined organisation of his day. He was either working at full stretch with little time to spare ('standing around in groups is not one of my hobbies') or relaxing with his family at home. Horse riding was his main form of exercise in middle age, though he had been a keen rugby and squash player in his youth.

As a result of his extremely busy life he was unintentionally a slightly distant figure in the larger family of ophthalmology but much admired for his dependable opinion and as a generous donor of sound advice; indeed he was rightly regarded as a pillar of British ophthalmology. When he retired from his hospitals in 1969 he continued to conduct his private practice and serve as hospitaller of St John Ophthalmic Hospital. This voluntary work away from the rivalries of a competitive life gave him much inner satisfaction and peace of mind.

He has survived by his wife Jane, who supported him in all his activities, one son, and three daughters. SM

A N Cameron, MB, ChB, FRCSEd, DOMS

Angus Neilson Cameron, who died 19 February 1987, was until his retirement in 1968 consultant ophthalmologist to Lichfield, Tamworth, and Sutton Coldfield and Wolverhampton Hospital Groups. He had spent his early life in Sunderland and Belfast before coming to Merseyside, where he attended the Merchant Taylors School at Crosby before entering Liverpool Medical School in 1921.

Following the literary tradition of his family, he edited the student journal *Sphinx*, and his regard for medical literature remained important throughout his life. After hospital appointments in Liverpool and visiting Australia he entered general practice in Derbyshire, where he had personal experience of the hard life of a mining community.

At the age of 46 years he returned to his special interest in ophthalmology and was elected to the Fellowship of the Royal College of Surgeons, Edinburgh, in 1950. In 1951 he was appointed consultant to Lichfield and Tamworth Hospital Groups with operating sessions at the Wolverhampton and Midland Counties Eye Infirmary. He became an active member of the Committee of the Eye Infirmary and will be remembered for his gentle and constructive approach to the solution of difficult problems. He was a faithful colleague and as loyal to the traditions of good medical practice as to his Highland ancestry.

In 1932 he married a fellow graduate, Winifred Walls, who died three years ago, a loss he felt deeply. There were no children. DFW

Book reviews

Glaucoma. Eds. James A McAllister and Richard P Wilson. Pp. 278. £55.00. Butterworth: Sevenoaks, Kent. 1986.

Glaucoma, like the poor, will always be with us. As with any familiar subject the very constancy of its presence means that it tends to be ignored. The old familiar methods of diagnosis and treatment are always relied upon, and nothing is new. Yet changes are occurring, and, as the editors here point out, in recent years 'new methods of interpretation, analysis and investigation' have led to a better understanding of the pathogenesis and early changes in the development of primary open angle glaucoma. These authors bring to our attention the observations by a number of writers whose aim it is to show us what is new in their respective fields.

What do these writers tell us? The chapters by Grierson, Quigley, and Greve on the outflow apparatus, optic nerve, and visual function are essential reading for all ophthalmologists. In these review articles the writers give first hand accounts of the advances that have been made in their subjects and do so with clarity and precision. By comparison some of the other chapters reveal that little change has occurred over many years. In particular the chapter on 'Congenital glaucoma' would suggest that no change has occurred in the diagnosis and management of these diseases over the last 10 to 15 years (as shown by the references and the standard illustrations). Other chapters on medical and surgical treatment are more encouraging, though the pace of change has, perhaps of necessity, been less dramatic than in the basic glaucoma sciences.

A book of this nature is bound to be selective. This reviewer would like to have seen chapters on the analysis of the topography of the optic disc, more reference to 5-fluorouracil, perhaps some word on seton devices such as that introduced by Molteno, all of which have greatly helped us in the management of primary open angle

glaucoma. For the most part, however, the subjects are well chosen and largely bear out the editors' contention that the sub-specialty of glaucoma is changing rapidly. Doubtless in a few years time Butterworths will ask them to reorganise the book in view of the additional advances that have occurred in the interim. In the meantime this book is well worth reading and should form part of the continuing education all ophthalmologists need to undergo.

ROGER A HITCHINGS

Environmental Health Criteria 54: Ammonia. Pp. 210. Sw Fr 18-00. WHO: Geneva. 1986.

This handbook is the latest title in the Environmental Health Criteria series commissioned by the International Programme on Chemical Safety (IPCS), and it documents the known effects of ammonia on human health and the quality of the environment.

Prepared by a distinguished WHO task group, this report considers the environmental sources and levels of ammonia with respect to human exposure, the important effects on aquatic organisms, and the consequences of short and long term exposure. Atmospheric ammonia is principally derived from natural biological activity, but point sources from sewage treatment and industrial plants may give rise to local regional increases in concentration and contamination of surface waters. There are important toxic effects on aquatic organisms, in particular fresh-water fish, and they can present an important pollution problem. There is no evidence that ammonia is mutagenic in mammals or carcinogenic following long term exposure. Indeed ammonia does not appear to represent a direct threat to man except as a result of accidental exposure, with the familiar irritant or caustic effects. Exposure to ammonia in water supplies and food appears insignificant compared with the nitrogen intake through the diet available as metabolic ammonia. The effects of short term inhalation and oral exposure are described, but the ophthalmologist will be disappointed by the passing reference to the acute effects of ammonia on the eye. In general, the report makes interesting reading and there is clearly little room for complacency, since point source emissions of ammonia from urbanisation, industry, and farming when deposited in a sensitive environment can induce significant toxic effects on man and his environment.

ROBERT J COOLING

Human Ophthalmic Pathology. A Short Practice. By OA Jensen. Pp. 192 Dkr. 395-00. Munksgaard: Copenhagen. 1986.

The author is an ophthalmic pathologist with a rich experience based on personal study of specimens submitted to the Eye Pathology Institute in Copenhagen. With his expertise in clinical ophthalmology and long practice in lecturing to students in both ophthalmology and pathology, he is thus well equipped to compose an authoritative text acceptable to trainees in either discipline.

Before launching into a systematic, tissue-orientated account of the histopathology of ocular disease he provides an eminently practical and useful introductory section which tells the aspiring ophthalmic pathologist how to process and examine the eye and its adnexal tissues and how

to interpret a range of staining methods. Given the stated readership this is a most valuable inclusion, and, although there is some risk in writing at this level, the author has judged the matter nicely and the result is neither condescending nor overelaborate.

Within a fairly short space few disorders of importance are omitted, and there is a wealth of apposite illustrations, mostly of histological preparations. Those incorporated within the text are in monochrome and are of generally acceptable, if not outstanding, quality, but an appendix provides helpful colour representations of the several staining reactions to which the text alludes. The text itself is concerned principally with histological descriptions and cannot often be faulted.

If there is a criticism it is that from the ophthalmologist's point of view a little more emphasis on the biological nature of the various lesions and their expected behaviour might have been useful. This is particularly relevant in respect of diseases, such as the non-neoplastic disorders of the retina, in which histopathological examination is rarely necessary to establish the diagnosis and is put to best advantage, if used, to derive an improved understanding of the disease process. Correspondingly, purely descriptive accounts in such circumstances are of little avail unless there is some attempt to explain how the changes come about.

But one cannot have everything without expansion in space and cost, and this is an intentionally short and moderately priced book. The above criticism is offered in a constructive spirit relevant to the future editions which must surely come, because it is much the best short book on the subject at present available.

ALEC GARNER

Textbook of Glaucoma. 2nd Edn. By M Bruce Shields. Pp. 549. £83-00. Williams and Wilkins: London. 1987.

For many years the world of glaucoma was dominated by two standard textbooks '*Lecture notes in glaucoma*' by Chandler and Grant, and Becker and Shaffer's '*Diagnosis and therapy of the glaucomas*.' Both offered in a single volume information about the whole subject of glaucoma. The former was characterised by a personal approach, cases histories, and no illustrations, while the latter was illustrated with good quality photographs, diagrams, and graphs crisply laid out and fairly didactic. Residents and glaucoma fellows used one (or both, for their emphases differed) for all essential information on the glaucomas. These books were the launching pads into the universe (field ?) of glaucoma. These two standard books have now been joined by a third, '*Textbook of Glaucoma*' by M Bruce Shields.

The 'Textbook' (as it will surely become known) arose out of an earlier '*Study guide for glaucoma*' and is slightly misleadingly shown as a second edition. The textbook may be seen as an updated expanded volume of the study guide which has so outgrown its predecessor as to merit more than the term 'revised edition.' Using a standard chapter format the author covers the whole of the subject in just over 500 pages. Each chapter begins with an overview (summary) providing a framework for the beginner. The style is easy to follow and well written. The text and opinions are backed by 3950 references (up to July 1985), so that the book will act as

an important reference source for further reading in any aspect of the glaucomas. The text is enhanced by many diagrams of good quality and black-and-white photographs which are passable (for they are often reprinted from original articles and lose not only colour but clarity in the transfer). The textbook will join 'Lecture notes' and 'Becker—Shaffer' as one of the three standard glaucoma texts. Every practising ophthalmologist should read one of them. For those requiring the references included here the 'Textbook' is the one to own.

ROGER A HITCHINGS

The Myopias. By BRIAN J CURTIN. Pp. 495. US\$ 75.00. Harper and Row: Philadelphia. 1985.

This work bids fair to become the authoritative source book on the literature of myopia. Written by one whose life-long clinical interest has been in the subject and who has made important contributions to the surgical technique of scleral support, it ranges widely over every aspect of its subject. The commonly encountered myopias are divided into three groups, physiological or correlation myopia without any axial elongation; intermediate myopia, a newish term in

which axial elongation is indicated by the presence of a crescent bordering the disc; and pathological myopia, wherein posterior staphyloma is the distinguishing characteristic. The aetiology, pathogenesis, and treatment are considered for each of these groups. Finally the related myopias, as for example those of prematurity or that are drug induced, are reviewed.

As the book is a bringing together of the opinions of many workers in the field both historical and recent, it is not to be expected that the author will come down decisively on the side of some particular standpoint over a controversial issue. The reader should not therefore expect any easy answers to such thorny questions as the predictability of progression, the relevance of close work, the stabilising effect of contact lenses, and other unsettled problems. The encyclopaedic style of the text has indeed reduced what might in some cases have been an appropriate sense of perspective in some sections, where perhaps a little more weight could have been given to the more accepted viewpoints. In spite of this the work must become part of the personal literature of all who are interested in the optical anomalies of the eye.

J D ABRAMS

Notes

European Ophthalmic Pathology Society

The 26th Annual Meeting of the Society was held in Peebles, Scotland, on 26–29 May 1987 at the invitation of Professor W R Lee. Dr M S O Tso of Chicago and the Verhoeff Society was the honoured guest. Papers relating to pathological case studies were presented by the 29 attending members and seven invited guests. They were as follows. Ocular manifestations of rabies (A Tarkkanen, Finland). Round cell liposarcoma of the orbit (K Arnesen, Norway). Choroidal metastasis of bronchial carcinoid (E Balestrazzi, Italy). Astrocytoma of the chiasm (M Brihaye, Belgium). Osteoma of the frontal sinus (A Brini, France). Laser photocoagulation of the retina (J Cunha-Vaz, Portugal). Proton-beam irradiated malignant melanoma (B Daicker, Switzerland). Keratoconus posterior circumscriptus (P Donders, Netherlands). Neurothekeoma (?) of the orbit (A Garner, UK). Basal-cell carcinoma of the conjunctiva (G Goder, GDR). Granular cell tumour of the orbit (R Haddad, Austria). Delayed lens-induced inflammation (A Hamburg, Netherlands). Haemangioma of the optic disc (M Hanssens, Belgium). Ocular leishmaniasis in the dog (A Heriques, Spain). Agenesis corneae (O Jensen, Denmark). Neurofibroma in the choroid of a neonate (E Kock, Sweden). Endophthalmitis haemosiderotica (E Landolt, Switzerland). Bulbar conjunctivitis (G Lang, FRG). Diffuse iris melanoma (Z Latkovic, Yugoslavia). Photoreceptor atrophy in an infant (W Lee, UK). Degenerative changes in the peripheral retina (M Matsuyama, Japan). Adeno-

carcinoma of the ciliary body (J Mullaney, Ireland). Papilloma of lacrimal drainage system (P Naeser, Sweden). Spontaneous haemorrhage from an anterior segment naevus (G Naumann, FRG). Macular corneal dystrophy (B Nicolaissen, Norway). Mucoepidermoid tumour of the lacrimal gland (J Prause, Denmark). Brucella endophthalmitis (M Quintana, Spain). Reactive lymphoid hyperplasia with functional atypia (A Rahi, UK). Retinal gliosis (J Sahel, France). Kearns-Sayre syndrome (G Stefani, FRG). Lattice corneal dystrophy (I Suveges, Hungary). Mesectodermal leiomyoma of ciliary body (M Tso, USA). Sarcoidosis of the lids and conjunctiva with corneal perforation (M Vogel, FRG). Post-traumatic granuloma (F Weber, Switzerland). Unclassified corneal mucopolysaccharidosis (H Witschel, FRG).

At the business meeting Dr J Mullaney was elected President for the next three years and Drs J Libert (Belgium), H Volcker (FRG), and D de Wolff-Rouendaal (Netherlands) were elected to membership. Dr M Hanssens (Belgium) is the new Corresponding Secretary.

Oxford Ophthalmological Congress 1988

The Oxford Ophthalmological Congress will be on 3–6 July 1988. Applications for free papers are invited. Abstracts should be sent to Mr J F Talbot, FRCS, Honorary Editorial Secretary, Eye Department, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, to arrive no later than 1 December 1987.

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Indication: White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses:** Topical ophthalmic suspension for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye. **Dosage and Administration:** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 3 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contraindications, Warnings, etc. CONTRA-INDICATIONS:** Acute superficial herpes simplex keratitis. Fungal diseases of the cornea, eye, vagina, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to any of the constituents of this medication. **Warnings:** Steroid medication in the treatment of herpes simplex keratitis involving the cornea requires great caution. Frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the cornea, defects in visual acuity and fields of vision, posterior or subcapsular cataract formation, or may aid in the establishment of any ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or perforation has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in children of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in contact with hydrophilic contact lenses. **Use in Pregnancy:** Safety of the use of topical steroids during pregnancy has not been established. **Precautions:** As fungal infections of the cornea are particularly prone to develop concomitantly with long-term steroid use, fungal invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra-ocular pressure should be checked frequently. **Adverse Reactions:** Glaucoma with optic nerve damage, visual acuity or field defects, or subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the cornea.

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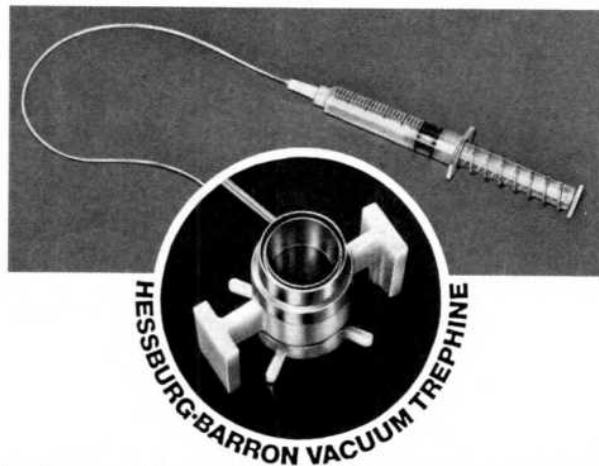
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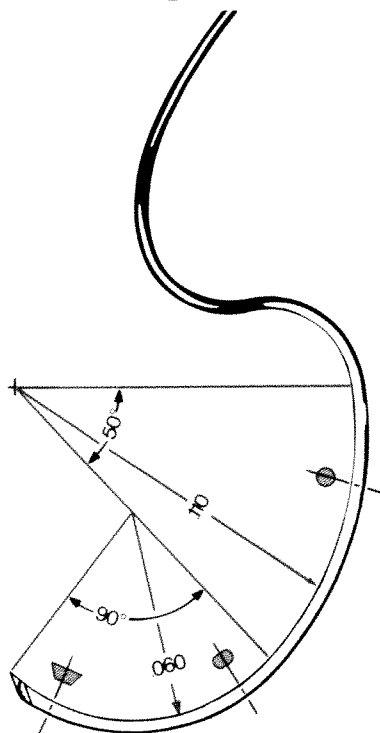
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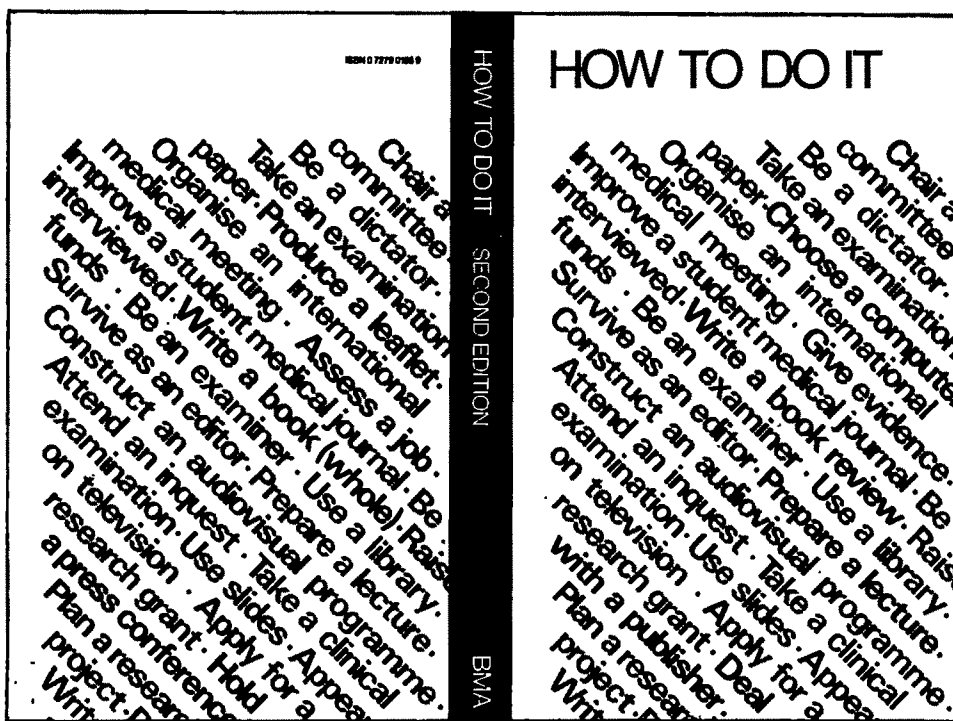
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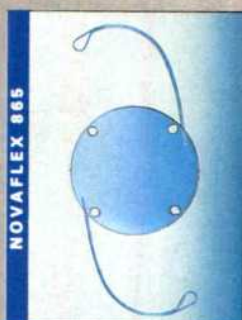
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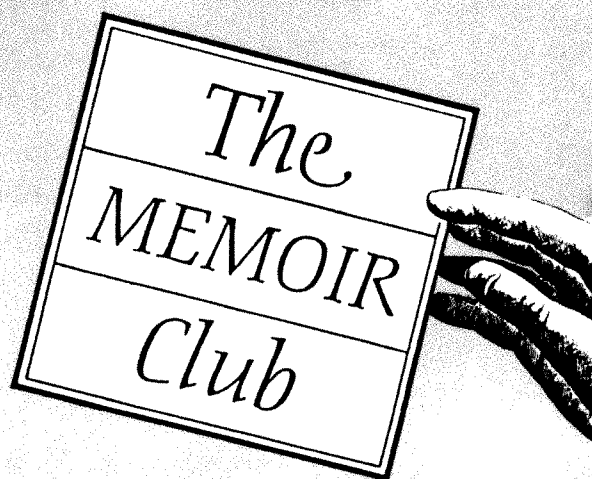
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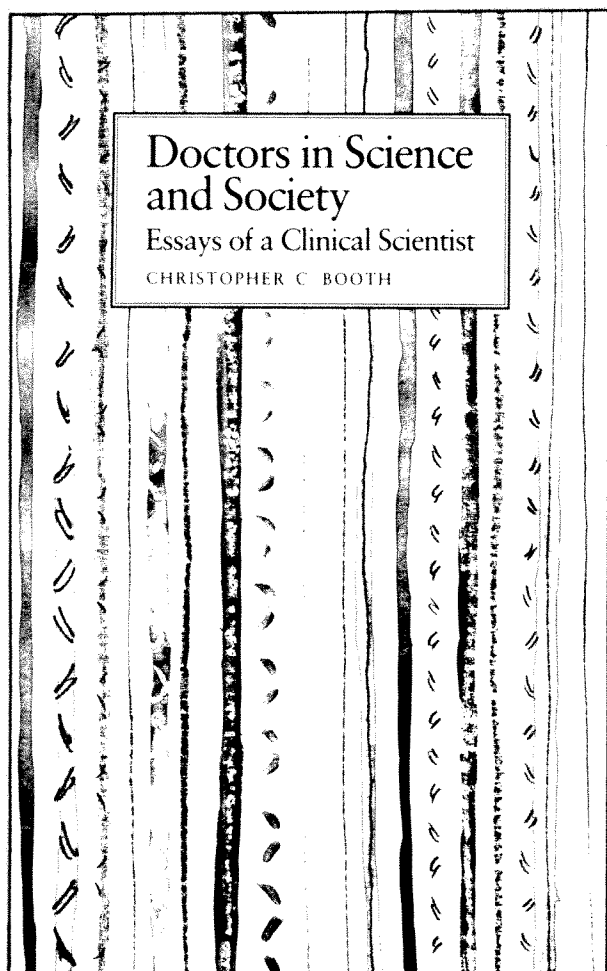


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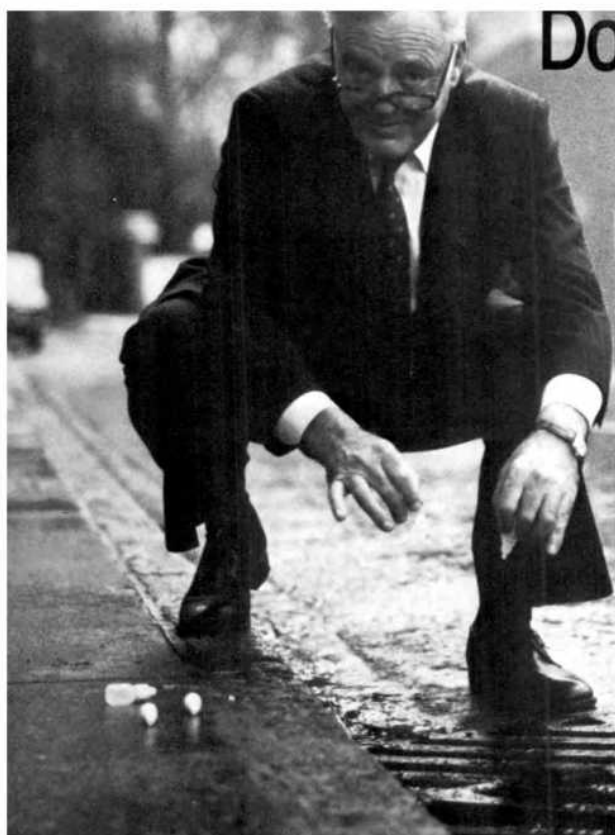
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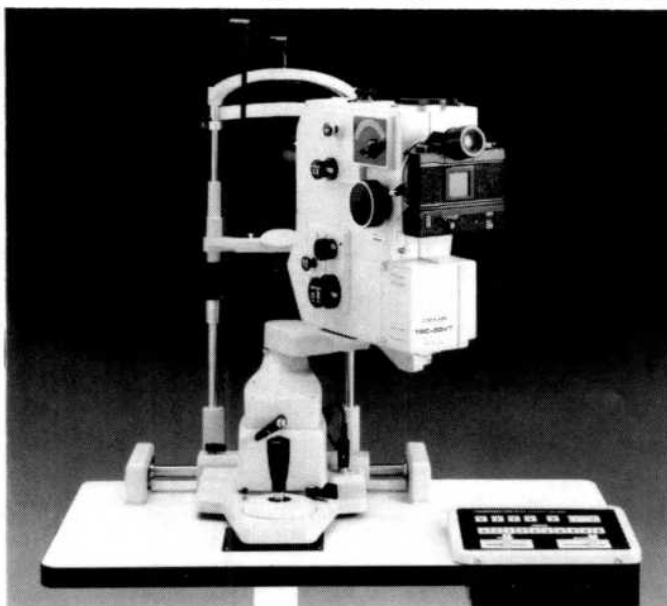
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References

1. Hopkins, G.A., *Am J Optom Physiol Opt*, 1985, **62**, (2), 132-141.
2. Demmler, N., *Der Augenspiegel*, 1980, 238-243.
3. Lichter, P.R. et al., *Amer J Ophthalmol.*, 1978, **85**, (4), 495-502.



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Ophthalmic zoster: mucous plaque keratitis

R J MARSH AND M COOPER

From the Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY Data taken from 1221 patients attending the Zoster Clinic of Moorfields Eye Hospital over the past 15 years were used to characterise the clinical appearance and behaviour of zoster mucous plaque keratitis (MPK). The typical greyish branching plaques are usually accompanied by a limbitis, stromal keratitis, or decrease in corneal sensation and are commonly associated with cataract, raised intraocular pressure, or corneal ulceration. MPK may begin at any time within two years of onset of the rash, but when it appears after three months there are more complications. Usually MPK settles within one month if appropriate treatment with topical steroids and acetylcysteine drops is given, but surgical intervention is sometimes required to control glaucoma or neuroparalytic keratitis or to remove cataracts. The results of surgery are surprisingly good.

Dendriform corneal epithelial disturbances have long been recognised in ophthalmic zoster but only relatively recently described in the literature.¹⁻³ The collective term 'pseudodendrite' precludes a satisfactory classification of these disturbances, gives no indication of the nature of the lesion, and is unhelpful in their management.

There are two distinct entities. The first, acute epithelial microdendrites, occurs a few days after the rash and resolves rapidly without complications. Viable virus is recoverable from the lesions.¹ The second, mucous plaque keratitis, by contrast has no clear temporal relationship to the rash and is a chronic disorder which is commonly associated with severe ocular sequelae such as glaucoma, cataract, and neuroparalytic ulcers.^{4,5} Viable virus cannot be identified in the lesions.⁴ The white-grey plaque which characterises the keratitis is adherent to the surface epithelium, has sharply demarcated margins, and may be linear or branched. There are usually several, which vary in size, shape, position, and number day by day, with no preferential corneal site. They stain sparingly with alcian blue, moderately with fluorescein, and brilliantly with rose Bengal (Fig. 1). They are deposited on a diffusely thickened and abnormal epithelium. Their onset varies from one week to two years after the rash. They are usually accompanied by a limbitis, stromal keratitis, diminished corneal sensation, or iritis and may be preceded by an episcleritis, disciform keratitis, or

iritis. Debridement of the plaque leaves an intact but abnormal epithelium.

Mucous plaques also occur with filamentary keratitis, keratoconjunctivitis sicca, superior limbic keratitis, vernal keratitis, varicella keratitis,⁶ and rarely with herpes simplex.⁵ The aim of this study is to define the clinical behaviour of zoster mucous plaque keratitis, to emphasise the difference from herpes simplex keratitis, to plan logical management and to report that the complicating glaucoma, cataract, and neuroparalytic ulcers may be successfully treated surgically.

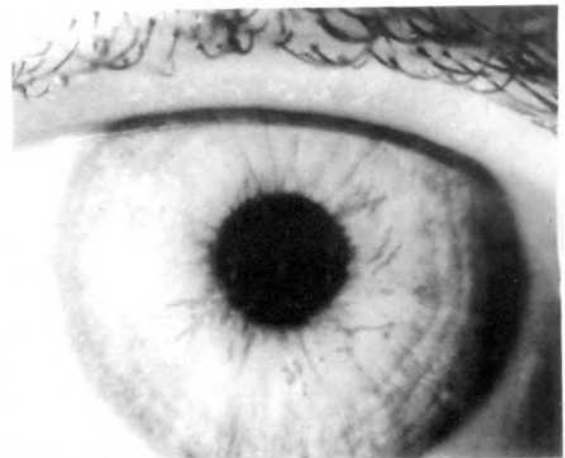


Fig. 1 Mucous plaques stained with rose Bengal.

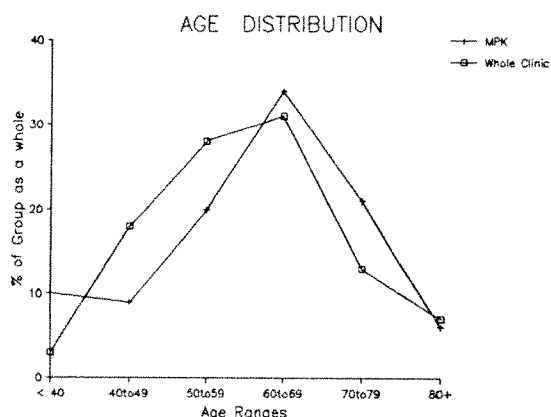


Fig. 2 Age distribution of MPK patients compared with that of the whole clinic.

Patients and methods

The data are derived from patients attending the Zoster Clinic at Moorfields Eye Hospital over the past 10 years, of whom the majority were primary referrals. Their follow-up has been regular and consistent over this period. Corneal sensitivity was measured with the aesthesiometer of Luneau and Coffignon in four peripheral sectors and centrally. The information was put on computer storage. 1030 patients (85%) had follow-up visits at least three-monthly over two years, and these form the study group. We compared the accompanying features of MPK with those of all ophthalmic zoster patients (with similar follow-up).

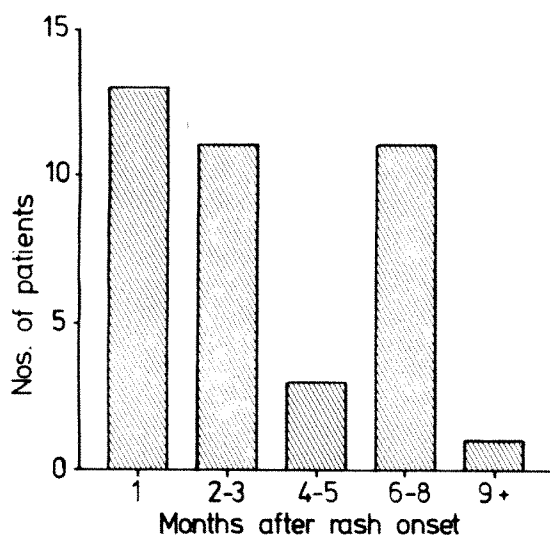


Fig. 3 Time of onset of MPK.

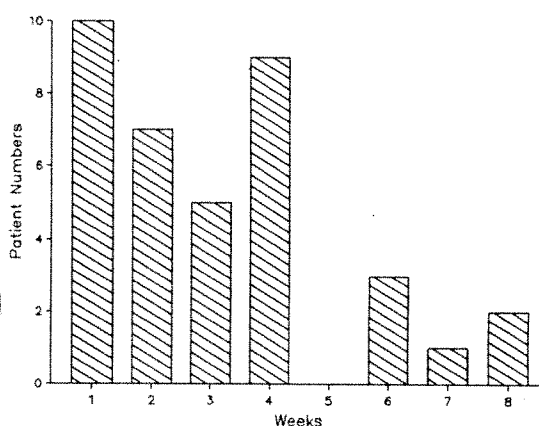


Fig. 4 Duration of MPK.

Results

Forty-seven (4%) cases of mucous plaque keratitis were found, of whom 39 had reliable follow-up data for two to 13 years (mean six years). Compared with the whole clinic population the patients with MPK were on average younger (Fig. 2). Fig. 3 shows the time of plaque onset in relation to the rash, the majority occurring within the first three or between six and seven months. Fig. 4 shows the duration of the plaque, which was usually less than one month.

Associated clinical features may be considered under the following headings: those preceding the onset of the plaque, those associated with it, and those subsequent to it.

There were no preceding features in 28%, but a complication distinguishing them from the rest of the clinic population was an increase in hypertensive iritis (Table 1; $p < 0.05$ by χ^2 test).

MPK is associated with a combination of episcleritis (usually perilimbal), iritis, superficial corneal stromal infiltration, and a decrease in corneal sensation, though none of these taken individually is more

Table 1 Incidence of associated clinical features occurring before and simultaneously with MPK. The incidence of these features in the clinic as a whole is shown in the last column

Category	Previous involvement	Coincident involvement	Overall clinic incidence
Iritis	22 (56%)	20 (51%)	50%
Raised IOP	16 (41%)	9 (23%)	14%
Episcleritis	12 (31%)	22 (56%)	59%
Diminished corneal sensation	14 (36%)	14 (36%)	33%
Keratitis			
Microdendrite	9 (28%)	0	20%
Nummular	13 (33%)	15 (38%)	49%
Disciform	7 (18%)	4 (10%)	12%
Oedema	7 (18%)	?	5%

Table 2 Incidence of clinical features following MPK

Category	Early plaque <3 months	Late plaque 3 months or more	Overall clinic incidence
Corneal stromal haze	16 (67%)	15 (100%)	?
Ulcers	2 (8%)	4 (27%)	4%
Diminished sensation	6 (25%)	9 (60%)	33%
Disciform keratitis	6 (25%)	5 (33%)	12%
Lipid keratopathy	4 (17%)	2 (13%)	5%
Lens opacities	10 (42%)	12 (80%)	12%
Refractory glaucoma	1 (4%)	5 (33%)	3%
Recurrence	6 (25%)	5 (33%)	4%

common in mucous plaque keratitis than in the clinic population as a whole (Table 1).

The sequelae can be split into two groups: one with plaque onset within the first three months and the other after this time. In Table 2 they are compared with the incidence of eye complications in the clinic population as a whole.

Table 2 indicates a generally more severe outcome in plaques of later onset except with respect to lipid keratopathy, disciform reactions, and uveitis. There is a greatly increased tendency to recur, a very frequent occurrence of diffuse anterior stromal haze, diminished corneal sensation, neuroparalytic ulceration, glaucoma, and cataract ($p < 0.05$ by χ^2 test). Only one case had a coincident herpes simplex infection. Two patients rapidly developed large interpalpebral ring-shaped subepithelial plaques with underlying stromal thinning (Fig. 5). These complications often led to visual loss (Table 3). Most of the morbidity was due to cataract and the remainder to various degrees of corneal scarring.

MANAGEMENT

The active keratitis was treated with topical steroid, the dosage being matched to the degree of inflamma-

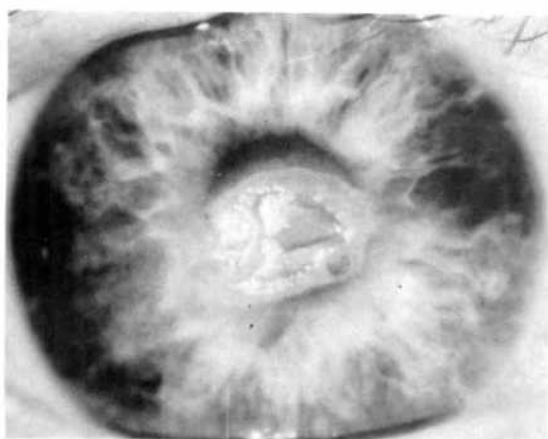


Fig. 5 Ring-shaped subepithelial plaque.

Table 3 Numbers of patients with decreased Snellen visual acuity (lines)

Lines lost	No of patients
0	11
1	5
2	7
3	3
4	3
5	10

tion (we graded episcleritis, keratitis, and iritis on a scale of 0–6). We started with dexamethasone 0.1% eyedrops four-hourly and, as the condition ameliorated, reduced the frequency over two months by degrees to twice daily. If control was maintained, the drop was changed to betamethasone, but any later recurrence necessitated returning to dexamethasone immediately. Over the next six months we tried to substitute prednisolone 0.3% eyedrops three times a day. Most cases subsided after this period but required a maintenance dose for long term use because there was a pronounced tendency for relapse even after two years, especially on reducing treatment or even on stopping prednisolone drops 0.3% once daily. Acetylcysteine 10% eyedrops dissolved the plaques, and artificial tears helped maintain the precorneal tear film. Timolol eyedrops were successful in most cases in controlling raised intraocular pressure due to iritis and steroids. Topical idoxuridine, adenine arabinoside, and trifluorothymidine made the epithelial problem worse, and acyclovir had no effect on this keratitis.

Two patients developed severe cataract and glaucoma which required surgical treatment. Neuroparalytic ulcers developed from one month to three years after MPK onset and were always treated with a lateral third tarsorrhaphy. Table 4 depicts the number of cases requiring surgery. In the three cases requiring glaucoma surgery it was successful in controlling intraocular pressure without antiglaucoma therapy, and the acuities of those patients who also had intraocular lens implants were 6/9. All cases required a booster dose of topical steroid over three months postoperatively because of relapsing iritis. The tarsorrhaphies were followed by healing of corneal epithelial ulcers within three days.

Table 4 Cases requiring surgery

Operation	No
Combined trabeculectomy + extraction + implant	2
Trabeculectomy	1
Laser trabeculoplasty	1
Lateral third tarsorrhaphy	5

Discussion

These results indicate that mucous plaque keratitis associated with herpes zoster ophthalmicus has a distinct clinical appearance and evolution. MPK is not difficult to diagnose if an adequate history is obtained. Although the appearance is superficially similar to that of herpes simplex, detailed examination of the morphology and of the staining characteristics will distinguish them. In our experience it is very rare to have coincident zoster and simplex. If there is doubt, a two-day intensive course of topical steroids will usually settle the inflammatory component of mucous plaque keratitis and obviously aggravate simplex dendrites. MPK is a self-limiting condition, but, while the inflammation may soon settle, the epithelium may take much longer to recover, especially if there is loss of corneal sensation or a degree of exposure.

At least two factors are likely to lead to MPK: altered corneal epithelium and disturbance of tear film mucus.⁷ Normal epithelium has mucous receptors primarily involved in the maintenance of the tear film. Alteration of these could reasonably lead to an accumulation of mucus, especially if the mucus derived from goblet cells is less soluble than usual. The entire corneal epithelium appears abnormal,³ as probably is the conjunctival epithelium. This may be due to infection, exposure, inflammatory mediators, and denervation with loss of 'trophic factors', all of which may lead to alterations in cell surface properties. The changing shape, size, and distribution would support the concept of a generalised abnormality that is quite different from the local lesions of acute herpes simplex keratitis, but more akin to those seen in keratoconjunctivitis sicca (although morphologically distinct). The subsequent diffuse stromal haze and decrease in corneal sensation would lend support to this hypothesis.

There are two groups: one with early onset (within the first three months of the rash) and the other with late onset. The latter group of patients have the more severe problems, such as cataract, raised intraocular pressure, and corneal ulceration. The high risk of recurrence may necessitate repeated observations and prolonged topical steroids. Posterior subcapsular lens opacities can arise from both chronic iritis and long-term topical steroid, but steroid is not recog-

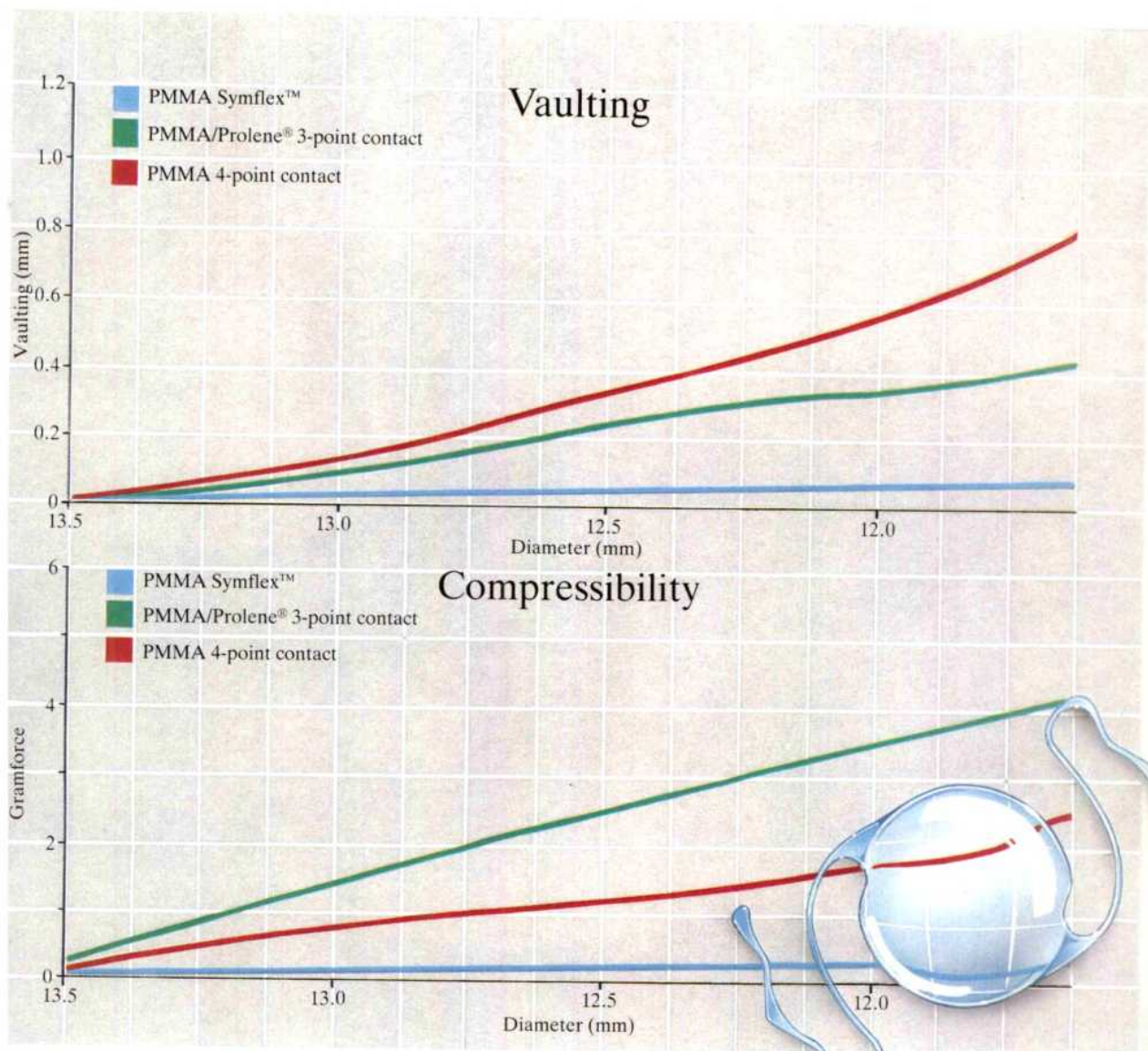
nised as giving rise to nuclear sclerosis. Raised intraocular pressure may be due to the necessarily intense and prolonged topical steroid treatment or a trabeculitis accompanying the iritis. An acute hypertensive uveitis will usually settle within a few days on thorough treatment with topical steroids, but if there is steroid-induced glaucoma the prednisolone is replaced by fluoromethalone and timolol eyedrops. With severe refractory glaucoma drainage surgery may be necessary. Continuing denervation of the cornea and conjunctiva leads to neuroparalytic keratitis and ulceration, which is compounded by steroids in the absence of a tarsorrhaphy. The circinate plaque deposits are distinct from those described in corneal infections.⁸

The results of surgery were good in this series. A booster dose of topical steroid is required post-operatively after all intraocular surgery for at least three months. Neuroparalytic ulcers were completely healed within a few days of tarsorrhaphy. Usually a temporal third was sufficient but occasionally a middle third was essential, and it was important to maintain the topical medication. Despite traditional reservations about intraocular surgery in patients with complicated ophthalmic zoster and the relatively small number of cases, we were pleasantly surprised by our encouraging results.

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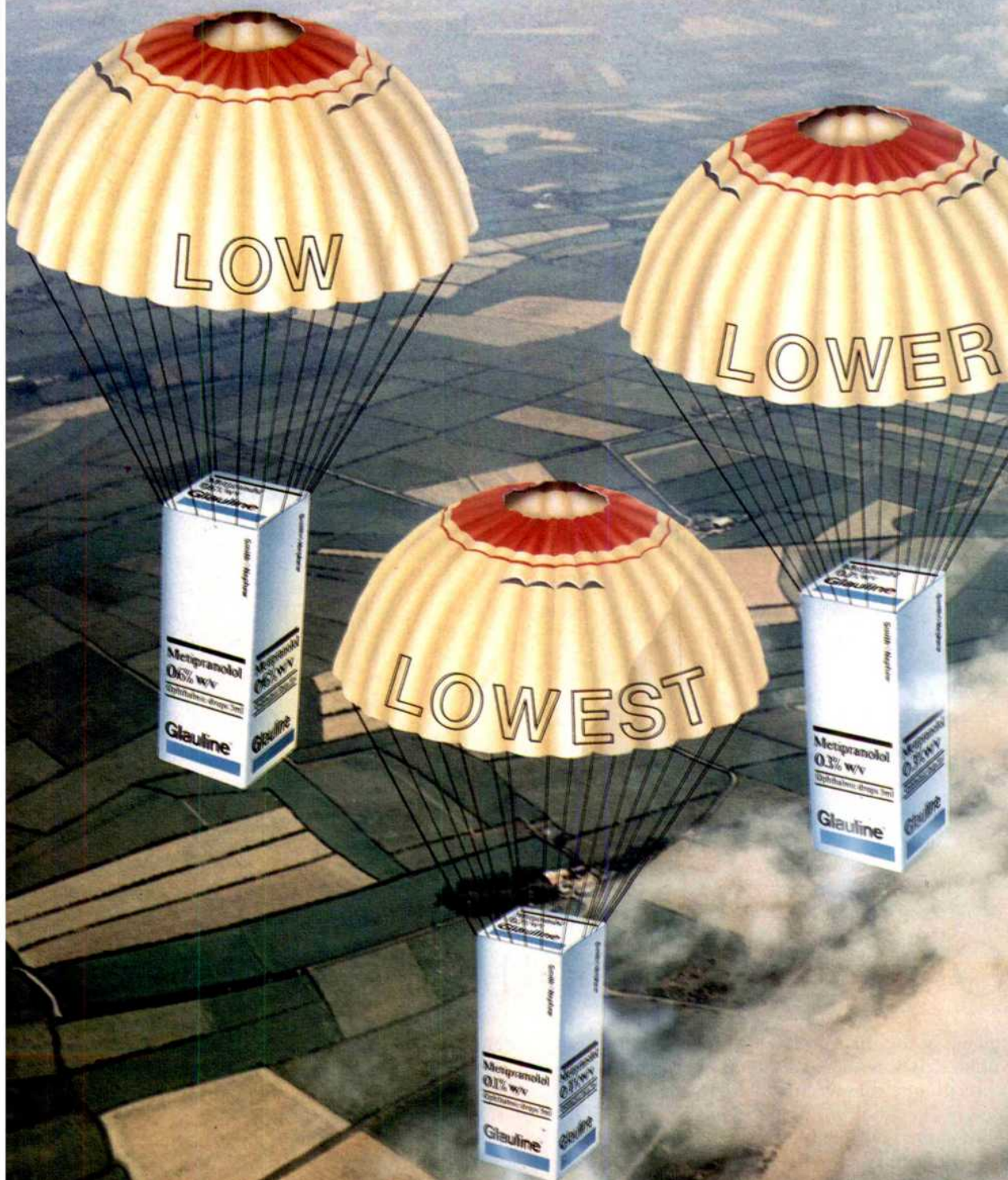
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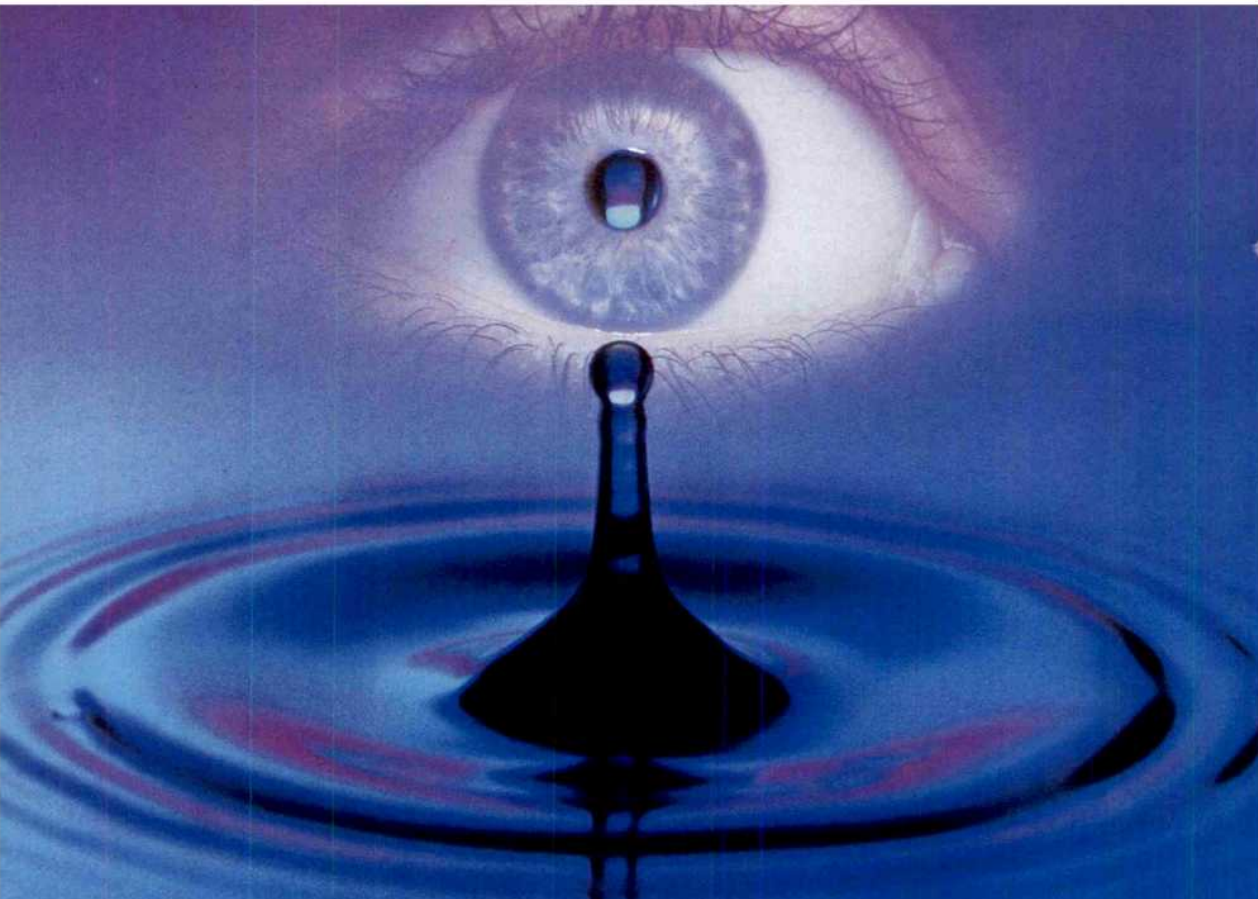
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Reference 1 Kralian I M. American Journal of Optometry and Physiological Optics 1986; 63 (No. 4): 304-308

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Morphological changes in the human corneal epithelium associated with surgical corneal clouding

S HAGUE, N DILLY, AND G M THOMPSON

From the Department of Ophthalmology, St George's Hospital, London SW17

SUMMARY Light microscopy and electron microscopy were used to define morphological changes occurring in human corneal epithelium during surgery. No correlation was established between preoperative medication or peroperative fluids and corneal epithelial clouding. It is suggested that the changes we observed in relation to epithelial clouding were the direct result of disturbance to endothelial pump functions.

Transient corneal clouding obscuring the view of intraocular structures during surgery has frustrated most ophthalmic surgeons. With the advent of closed intraocular surgical techniques observed through the operating microscope the effect has become more apparent. It has been known for many years that the obscuration is caused by the corneal epithelium. Surgeons have removed the epithelium of clouded corneas and restored a clear view. The effect seems more marked in diabetic patients, and Foulks *et al.*¹ suggested basement membrane abnormalities were a causative factor.

The normal cornea is approximately 78% water. The state of hydration rests on the balance between the hydrating forces (swelling pressure of the proteoglycan stromal matrix and intraocular pressure) and the dehydrating forces (endothelial and epithelial pumps and barriers, and surface evaporation).

The contribution of each of these factors needs to be examined in terms of its potential contribution to the genesis of the corneal oedema. It should be possible to detect the sites of accumulation of oedema fluid and of any associated cell damage. If we can identify the most significant factors involved in corneal oedema we may then be able to suggest ways of reducing their effects.

We have carried out a study of the anatomical changes in the corneal epithelium in 10 patients undergoing ophthalmic surgery.

Materials and methods

Patients attending St George's Hospital for ophthalmic surgery were assessed preoperatively. Previous ophthalmic surgery and intercurrent eye disease in addition to that for which surgery was planned were recorded. An inquiry was also made for systemic disease and topical and systemic medication. The patient's age was noted. Careful slit-lamp examination was performed with particular attention to the cornea. The intraocular pressure was also recorded.

A record was kept of the preoperative ocular medication each patient received. At the time of surgery records were made of the nature of the skin preparation used, the duration of corneal illumination, the nature, osmolarity, and volume of fluid used to moisten the cornea and also of that used in intraocular infusion and of any peroperative problems. The degree of corneal clouding was recorded as nil, mild, moderate, or severe at the preoperative examination and also at the beginning of surgery, during surgery, and at the end of surgery.

Small specimens of peripheral corneal epithelium were taken at the beginning and end of the surgical procedure. These were immediately transferred to appropriate fixatives for later examination with light and electron microscopes. Samples were collected from 10 patients—seven undergoing extracapsular extraction with lens implant, two intracapsular cataract extraction, and one lens aspiration. Specimens were fixed in half-strength Karnovsky's fixative pH 7.4 for 2–12 hours at 4°C. They were then washed briefly in several changes of 0.1 M sodium cacodylate-HCl buffer (pH 7.4 and postfixed in 2%

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osmium tetroxide made up in the same buffer for 1 h at room temperature. Specimens were then washed in 0.1 M sodium cacodylate buffer at pH 7.4, dehydrated in ethanol and propylene oxide, and embedded in Spurr resin. All sections were cut on a Sorvall MT2-B ultramicrotome.

Thick sections (1 μm) for light microscopy were cut with a glass knife and stained with either toluidine blue or crystal violet. Thin sections for electron microscopy were cut with a diamond knife, stained with uranyl acetate and Sato's lead, and examined in a Phillips 301 electron microscope.

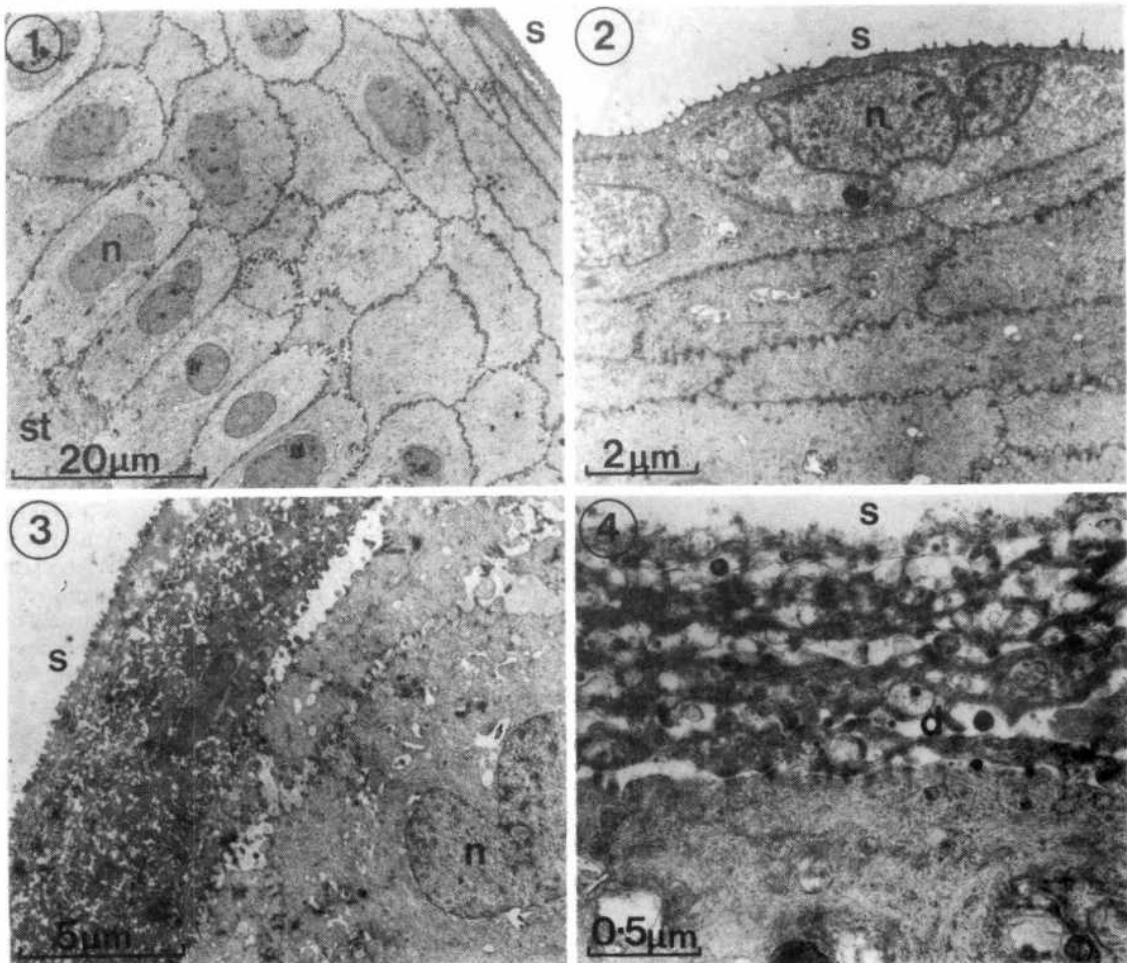
Cryofreezing was used as a control to check that the fixative techniques were not producing significant changes.

Results

Our results show that changes are produced in the corneal epithelial morphology during the course of eye surgery. These changes occur throughout the thickness of the epithelium, those near the stromal surface differing from those near the tear surface. These changes can be described in terms of cytoplasmic changes, cell/cell junction changes, and changes in the cell nucleus.

CYTOPLASMIC CHANGES

The layers of cells close to the tear surface show a reduction in cytoplasm and a separation of cell membranes, though the desmosomes and tight



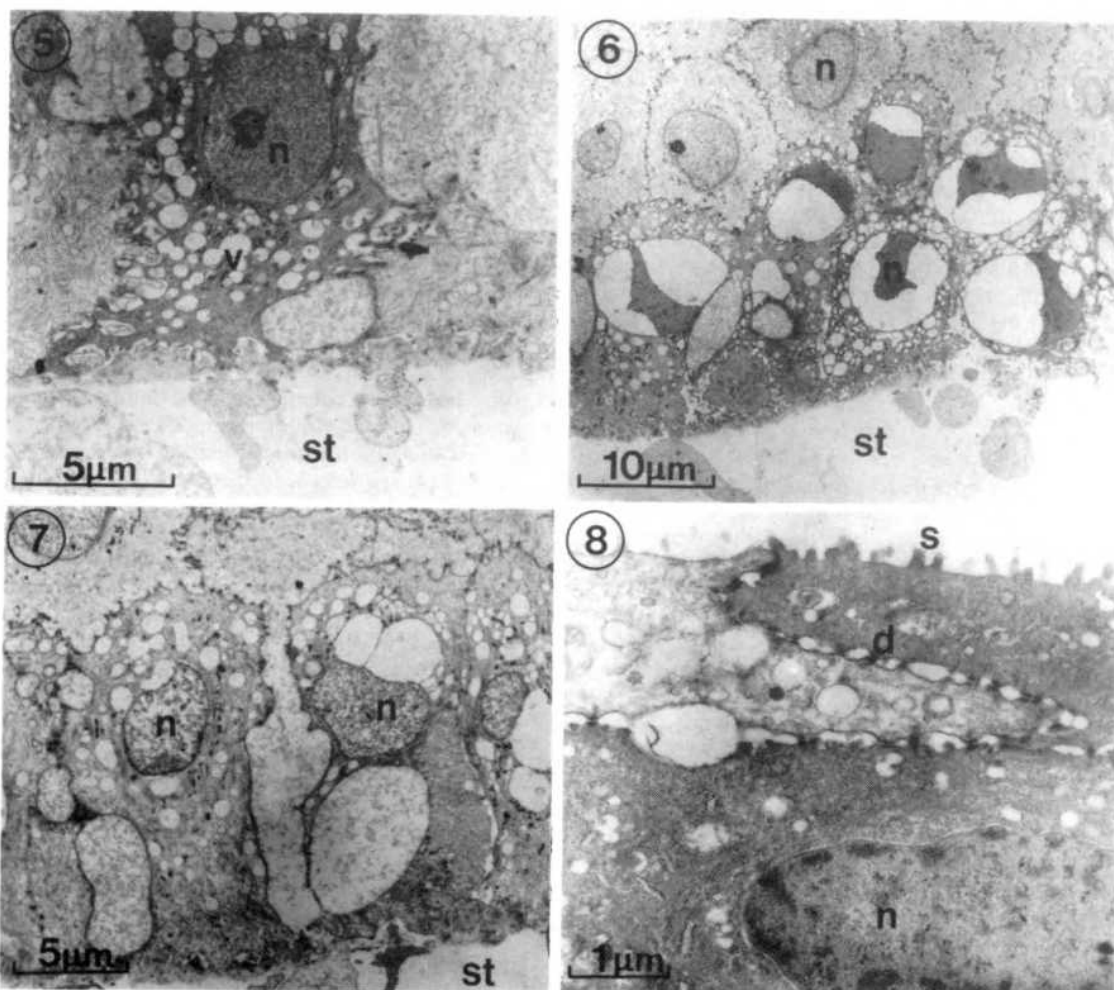
Figs. 1-4 Progressive destruction of the superficial layers of the corneal epithelium from Fig. 1 at the beginning of an operation to Fig. 4 at its end. st=Stroma (or stromal surface). s=Surface. v=Vesicle. d=Desmosomes. n=Nucleus.

junctions do not separate. The extreme of this condition is to have a stack of cell membranes separated by the remains of the cytoskeleton resting on the underlying cells (Figs. 1–4). The innermost layer of the epithelium, that is, the layer adjacent to the stroma, shows surprisingly different changes. Here the cytoplasm appears to remain intact, but there is an accumulation of vesicles within the cells (Fig. 5). These vesicles have electron lucent contents and are possibly membrane bound. They occur in large numbers. As the number of vesicles increase so the number of layers that contain them increase, starting at the basal layer and progressing upwards through the epithelium to the surface layers. These

changes are initially more severe in the dark cells (Fig. 5), but as the number of vesicles increases both light and dark cells become equally affected (Fig. 6). (Usually nuclear collapse does not occur widely until the light cells have begun to accumulate significant numbers of vesicles—Fig. 7.)

NUCLEAR CHANGES

The nuclei too respond differently according to their location in the epithelium. In the basement layer of cells the nucleus and nuclear membrane are collapsed away from the cytoplasm, thus leaving the outer layer of the nuclear envelope attached to the cytoplasm (Fig. 6). Some of the nuclear pores remain attached



Figs. 5–8 Fig. 5: Vesiculated dark cell of innermost layer of corneal epithelium with intact nucleus. Fig. 6: Nuclear collapse in the innermost epithelial layers. The outer layers still contain intact nuclei. Fig. 7: Exclusive dark cell vesiculation with intact nuclei in the innermost layer of the epithelium. Fig. 8: Outermost layer of corneal epithelium showing the desmosomes resisting cell separation. Symbols as in Figs. 1–4.

to the inner layer of the nuclear envelope. In the more superficial layers the nuclei are better preserved.

INTERCELLULAR SPACES

Contrary to some reports² we found that there is very little separation of the cells, and the expansion of the intercellular spaces seems to be limited by the desmosomal junctions (Fig. 8). This is in contrast to chronic oedema and to the oedema associated with infection where there is considerable expansion of the intercellular spaces (Dilly N, personal observations). In some specimens there appears to be herniation of some of the cell cytoplasm out of the cells. This occurs in epithelia that are not supported by stroma, and the herniation probably occurs through that part of the cell membrane that was attached to the underlying basement membrane by hemidesmosomes. It is possible that this change represents the mechanical trauma of stripping off the epithelium from the underlying stroma while the biopsy is taken.

We could not show any relationship between the observed morphological changes and the factors recorded preoperatively. Neither was there any apparent relationship to the type of surgery, type of skin preparation, peroperative intraocular or corneal fluids, or the nature or duration of the surgery or the surgeon.

Discussion

The human corneal epithelium has a great capacity for recovery from many insults, but not infrequently it fails to maintain its transparency during ophthalmic surgery. The transparency of the cornea is dependent on many factors, a very significant one of which is the state of hydration of the stroma and epithelium. The water within the cornea is in dynamic balance. The factors involved in this balance must include: evaporation from the surface, the swelling pressure of the cornea, the intraocular pressure, and the efficiency of the intracellular pumps. For oedema to occur this balance must be upset, so that water accumulates. This means that either water uptake is increased or water loss is decreased.

The major factor in the uptake of water is the stromal swelling pressure. The normal stromal swelling pressure is 40–50 mmHg. It will, of course, decrease as the oedema worsens because of the high water binding capacity of the proteoglycan stromal matrix. During surgery this must be the major factor responsible for the uptake of water into the cornea, as the contribution of the intraocular pressure will be to some extent eliminated by the surgical decompression of the globe. The swelling pressure is a result of

the matrix between the collagen bundles of the stroma, and it seems improbable that the surgical procedures can interfere with its activity. The factors that oppose this hydration are surface evaporation and the endothelial and epithelial pumps. Surface evaporation plays a minor role but may become important in compromised corneas. Surface evaporation will result in an increased tear tonicity and a resultant forward movement of water through the cornea. This osmotic extraction is thought to account for only 4% of the total dehydrating forces.

The adenosine triphosphate (ATP) dependent endothelial pump accounts for the bulk of the corneal fluid flow, pumping water from the cornea into the anterior chamber. Both the epithelium and the endothelium act as semipermeable membranes and bar the flow and diffusion of electrolytes but not the diffusion of water. The epithelium has a much poorer pump function but is a better barrier than the endothelium. Whatever the pump mechanisms, ions are pumped out and water follows. The surgical decompression of the globe will enhance this pumping mechanism. One of us (GT) has observed a correlation between the density of corneal clouding and the use of closed intraocular infusion during surgery. Clouding occurs shortly after infusion begins and clears when the instruments are removed. The closest part of the cornea to the infusion is the single layer of endothelial cells lining the inner surface of the stroma. It is tempting to postulate temporary disturbance of endothelial cell ion pumps as being responsible for the clouding. Since clouding of the cornea usually occurs after irrigation of the anterior chamber it is reasonable to speculate that the irrigation is interfering with pump function. Since the cornea is almost totally permeable to water, any failure of the electrolyte pumping mechanism will result in an accumulation of fluid within the cornea.

It is also necessary to consider other contributory factors such as the heat of the operating lights, preoperative ocular medications, and skin preparations.

We consider it is unlikely that the skin preparation affected the corneal epithelium adversely, since care was always taken to avoid any spillage into the conjunctival sac. MacRae *et al.*³ found in testing five commonly used skin preparations that only povidone iodine solution (without detergent) was non-toxic to the cornea. The majority of our patients received povidone iodine skin preparation.

During intraocular surgery saline or balanced saline solutions are frequently used to replace the tear film. During surgery for retinal detachment some surgeons have protected the cornea with gelatin sponge.⁴ The use of hyaluronic acid, possibly combined with a contact lens in closed vitrectomy, has

been advocated by Pruett *et al.*⁵ and Spencer *et al.*⁶. Norn⁴ studied peroperative protection in 221 consecutive cataract extractions and concluded that Healon was the most effective in preventing epithelial damage as assessed by vital staining with 1% lissamine green. However, four or five instillations of saline per half hour also satisfactorily prevented stromal deturgescence and associated corneal clouding. Methyl cellulose, polyvinyl alcohol, and a soft contact lens did not give any added benefits. However, we could not prevent corneal clouding by saline instillations alone. Our observations would suggest that most if not all of these procedures are irrelevant to the control of corneal clouding, though of course they may protect the corneal epithelial cells from other damage.

When we altered the osmolarity of the tear film substitute we did not observe any difference in the morphological changes we have described. We did record a 4°C temperature increase on the surface of the cornea in one patient between the beginning and the end of surgery. Other subjects showed a smaller rise. Again we found no correlation with the degree of corneal clouding. We believe that it is unlikely that the changes in epithelial morphology are due to light and/or heat damage caused by the operating microscope, since such temperature changes would produce very little extra evaporation from the eye surface.

The surprising finding from our work was the absence of large expanded extracellular spaces that contained oedema fluid. Such fluid filled spaces are well documented. In chronic epithelial oedema Lohman *et al.*² reported intercellular fluid accumulation in the basal layers. This has also been reported as a very early finding by Tripathi and Bron.⁷ Our findings probably represent the changes associated with the very recent onset of an acute oedema, not the more long-term changes previously reported. Presumably the conditions we describe could progress to mimic these descriptions.

Our report of these acute changes shows that the cells of the cornea can suffer severe morphological changes and yet recover their function.

We believe that our description is the first published report of the morphological changes occurring in the human corneal epithelium during surgery. Our findings have not shown any single factor to be responsible for these changes. Previous investigations of this subject have concentrated on direct toxic effects to the epithelium of changes in osmolarity, preoperative drops, or skin preparation. Attempts to protect the corneal epithelium should perhaps be focusing on protecting the functional integrity of the endothelium. The reason for this is that we suspect that transient changes in endothelial function are of greater significance.

We are grateful to Miss Celia Cope for her expert technical assistance and to Miss Melanie Coulton for secretarial help. We also wish to thank Sister C Burnell and the ophthalmic theatre staff at St George's Hospital for their co-operation with this study.

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Acanthamoebic keratitis diagnosed by paracentesis and biopsy and treated with propamidine

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SUMMARY A previously healthy 53-year-old man had keratitis of the right eye for six months, unresponsive to topical medical therapy. *Acanthamoeba* was grown from tissue obtained by corneal biopsy and from aqueous from an anterior chamber tap. The patient was treated with propamidine isethionate 0.1% drops and dibromopropamidine isethionate 0.15% ointment, and after two and a half months the ocular inflammation was continuing to resolve. This case supports a role for the diamidines in the treatment of acanthamoebic keratitis.

Acanthamoebic keratitis is a serious sight threatening condition. It can be difficult to diagnose and very difficult to treat. Despite an increasing number of reports ophthalmologists must base their knowledge of the condition on anecdotal reports of those cases which provide insight into the clinical problem. This report is of a man who had a persistent hypopyon from which the organism was recovered, and who responded to topical administration of propamidine isethionate and dibromopropamidine isethionate.

Acanthamoeba species have now been reported many times as having caused protracted keratitis unresponsive to medical therapy.¹⁻¹¹ Reports of successful medical treatment are few. Of these, one has been of treatment with a combination of propamidine isethionate drops 0.1%, dibromopropamidine isethionate 0.15% ointment, and neomycin drops¹² and another of treatment with topical miconazole 10 mg/ml, polymyxin-neomycin-gramicidin, and propamidine isethionate.¹³ The case reported here supports a role for diamidines in the medical management of acanthamoebic keratitis.

Case report

A healthy 53-year-old man was referred with right keratitis, unresponsive to treatment with topical prednisolone acetate 1% and acyclovir during the preceding month. He remembered no episodes of ocular trauma but had had an attack of keratitis four years previously which healed within two weeks of beginning topical antiviral therapy.

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On examination, visual acuity in the right eye was hand movements at 1 m, in the left eye 6/5. In the right eye there was a large central corneal epithelial defect overlying an area of stromal inflammation which extended to the corneal mid-periphery, where the opacification was denser (Fig. 1). Iris details could not be seen. Corneal scrapings grew *Staphylococcus epidermidis*, and topical treatment was continued with vidarabine ointment, prednisolone sodium phosphate 0.5%, and atropine 1% drops.

After five weeks the anterior segment inflammation had increased and a hypopyon was evident (Fig. 2). On several occasions during the next two months cultures for bacteria, fungi, and amoebae were negative, and the hypopyon persisted, accompanied by severe ocular pain. At the end of this time the

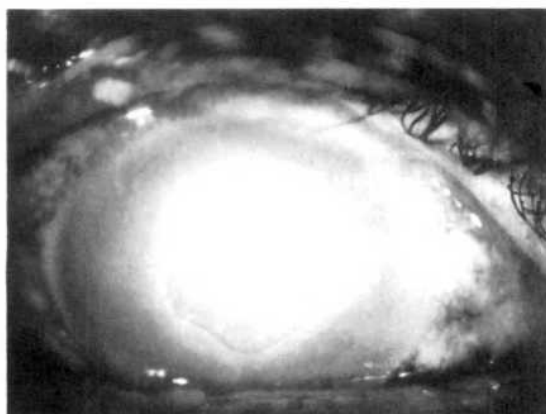


Fig. 1 Large central corneal epithelial defect overlying an area of stromal inflammation.



Fig. 2 Central keratitis with hypopyon.

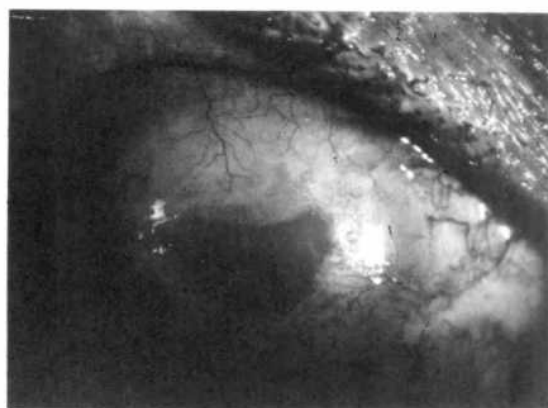


Fig. 3 Central epithelial defect stained with rose Bengal.

corneal opacity was dense, but the corneal epithelial defect had begun to heal and was completely epithelialised three months after the patient's initial presentation.

For the next two months the condition remained unchanged. At the end of this time aqueous from an anterior chamber tap showed unusual eosinophils but no causative organism. One week later, and six months after the onset of the keratitis, corneal biopsy was performed, with repeat anterior chamber tap. *Acanthamoeba* grew from both specimens after five days, though none was seen in the histopathological sections of the corneal biopsy. Morphologically, the organism was similar to but not identical with *Acanthamoeba polyphaga*.

Because of the extent of anterior segment inflammation and the presence of amoebae in the aqueous humour, medical treatment was preferred to surgical excision and corneal grafting. Treatment was started with propamidine isethionate 0.1% drops two hourly, dibromopropamidine isethionate 0.15% ointment at night, prednisolone acetate 1% drops every two hours, and atropine 1% drops twice daily.

After three weeks there were signs of improvement, with less anterior segment inflammation, disappearance of the hypopyon, and clearing of the stromal infiltrate and oedema, allowing some view of the iris details. This improvement was maintained during the next month; but, with recurrence of a central epithelial defect (Fig. 3), treatment was reduced to propamidine isethionate 0.1% drops and prednisolone acetate 1% drops, each four times a day, and atropine 1% drops twice daily. The eye was padded. The epithelial defect healed within one week, but further reduction of propamidine isethionate 0.1% to twice daily resulted in a rapid increase in anterior segment inflammation.

Subsequently the patient received propamidine isethionate 0.1% drops four times a day and dibro-

mopropamidine isethionate 0.15% ointment at night for two months, then the drops only for a similar period. Further reduction of treatment resulted in increased inflammation, but this tendency decreased with time and ocular inflammation continued to resolve. The eye is now quite comfortable, but visual acuity remains hand movements at 1 m, owing to corneal opacity and cataract (Fig. 4).

Discussion

Two aspects of this case are unusual. Firstly, *acanthamoeba* was recovered from the anterior chamber and disaggregated corneal material but could not be seen in a biopsy conducted by personnel experienced in identifying the organism. Secondly, a favourable response to medical therapy was apparent. In other respects the case represents a common clinical problem: a clinical picture at presentation assumed due to herpes simplex virus and an



Fig. 4 Appearance of the cornea six months after commencement of medical therapy for *acanthamoebic* keratitis. The epithelium has healed, but extensive stromal opacity and vascularisation remain.

encouraging healing of an epithelial defect in response to topical steroids, but with stromal inflammation continuing despite further topical medication. In this situation corneal biopsy needs to be considered, and the results can be most helpful, as in this case.

Acanthamoeba is a small, free-living organism commonly found in soil, fresh water, and sea water, and cysts can occur in airborne dust. Of all free-living amoebae, only *acanthamoeba* and *Naegleria fowleri* are pathogenic in man.^{14, 15} Two forms of the organism exist: cysts and trophozoites. The cysts are remarkably resistant to desiccation and heat, as well as to chemical disinfectants, but are killed by autoclaving or gas sterilisation.¹⁶ Both forms of the organism are also resistant to most antimicrobial agents,¹⁷⁻¹⁹ but cysts are more resistant than trophozoites and may persist in the cornea indefinitely, requiring prolonged topical therapy.²⁰

Although *acanthamoebic* keratitis is reported with increasing frequency, reports are anecdotal, and the outcome is often poor. There have been few indications as to what treatment might be expected to be effective, but the most promising has been with propamidine and dibromopropamidine isethionate.

Propamidine isethionate and dibromopropamidine isethionate are members of the diamidine group of drugs. They both have antibacterial and antifungal activity and have long been used for the treatment of blepharitis and conjunctivitis. Dibromopropamidine isethionate is available as a 0.15% ointment and is reported to be active against pyogenic cocci, *Staphylococcus aureus*, and Gram-negative organisms, including some strains of *Pseudomonas*.¹² Propamidine isethionate is available as 0.1% drops and has a reduced spectrum of antibacterial activity, being active against Gram-positive organisms, including staphylococci and *Streptococcus pyogenes*, but not against Gram-negative organisms.¹²

The diamidines are also toxic to a number of different protozoa, but their mechanism of action has not yet been established.²¹ Wright and colleagues¹² showed that propamidine and dibromopropamidine isethionate have acted in vitro against both cysts and trophozoites of *acanthamoeba* and that, clinically, there were no adverse reactions to these drugs during two months' treatment.

The case reported here further supports the place of propamidine and dibromopropamidine isethionate in the treatment of *acanthamoebic* keratitis and also emphasises the useful role of corneal biopsy in the diagnosis of this condition.

We gratefully acknowledge the assistance of Peter Christy and Bret Robinson of the State Water Laboratories, South Australian Department of Engineering and Water Supply, in identifying *acanthamoeba*.

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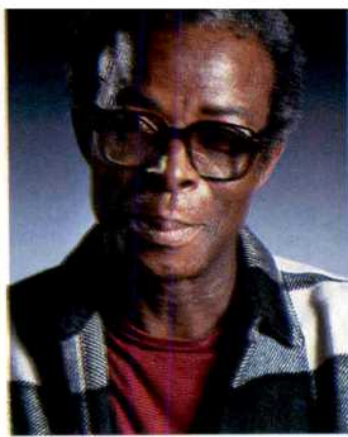
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Entoptic phenomena and reproducibility of corneal striae following contact lens wear

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SUMMARY Vertical corneal striae distributed across the posterior cornea are one of the objective signs of clinically unacceptable corneal swelling ($>6\%$) resulting from contact lens wear. This study reports that corneal striae are repeatable both in configuration and location with different levels of hypoxia. In most instances entoptic phenomena result from the presence of these lines. The results suggest that the healthy, avascular, transparent cornea has certain localised areas in its anatomical structure which may give rise to bundles of collagen fibres being made visible objectively and subjectively during conditions of corneal swelling.

Corneal striae is a term used to describe lines seen in the corneal stroma of varied appearance, aetiology, and pathology. Deep striae have been seen as a result of trauma (penetrating wounds),¹ after intraocular operations (striate keratitis),¹ in degenerative changes of collagen such as keratoconus,^{2,4} in diabetes,⁵ and in idiopathic⁶ corneal conditions. It is a well known clinical observation that vertical striate lines distributed across the posterior cornea are caused by corneal oedema accompanying hydrogel (soft) lens wear.^{7,8} The vertical or near-vertical striate lines, indicating the presence of 4 to 6% or more of corneal oedema,⁹ are reversible on removal of the lens.⁸ Striate keratopathy accompanies stromal swelling of about 7 to 10% or more, and appears as deep folds in the endothelial mosaic/Descemet's membrane area.^{7,8} The stromal lines can best be viewed against the dark background of the pupil with high light intensity from the slit-lamp biomicroscope by using direct focal illumination.^{6,9,10}

The reproducibility and entoptic phenomena of corneal striae were first noted by Johnson (reported by Johnson and Ruben¹¹) while investigating stromal oedema induced by soft gel lens wear.¹² The striae were induced by thick hydrogel lenses in normal adult corneae following three hours of wear in both the open and closed eye conditions. Photographic records were made of the appearance of the striae by retroillumination, and the similarity to the entoptic phenomena as recorded in a drawing by the indi-

vidual was strikingly similar. Furthermore, there was intrasubject repeatability of striae with large inter-subject variability of corneal striate lines.

In this paper we describe the repeatability and entoptic phenomena of corneal striae following contact lens wear and provide additional clues to its aetiology.

Material and methods

SUBJECTS

The study involved 11 volunteers with an age range of 23 to 36 years, consisting of nine males and two females. A second group of subjects seen after an interval of one year comprised five females and two males, with an age range of 21 to 30 years. All were free of any eye pathology and none had previously worn contact lenses.

To verify the first series of observations a second group of subjects similar to the first were studied. The experiment was to ascertain a qualitative finding and not measure in any degree the striae.

The illustrations (Figs. 1 and 2) are selected from those taken from one subject.

CONTACT LENSES

To induce corneal swelling greater than 6%, thick hydrogel lenses were worn by each subject. The lenses used in this study were 38-6% water content hydrogels (Metrosoft II - polymacon) manufactured by Metrosoft Incorporated (Austin, Texas). Two lenses were used, each having a base curve of 8.3 mm,

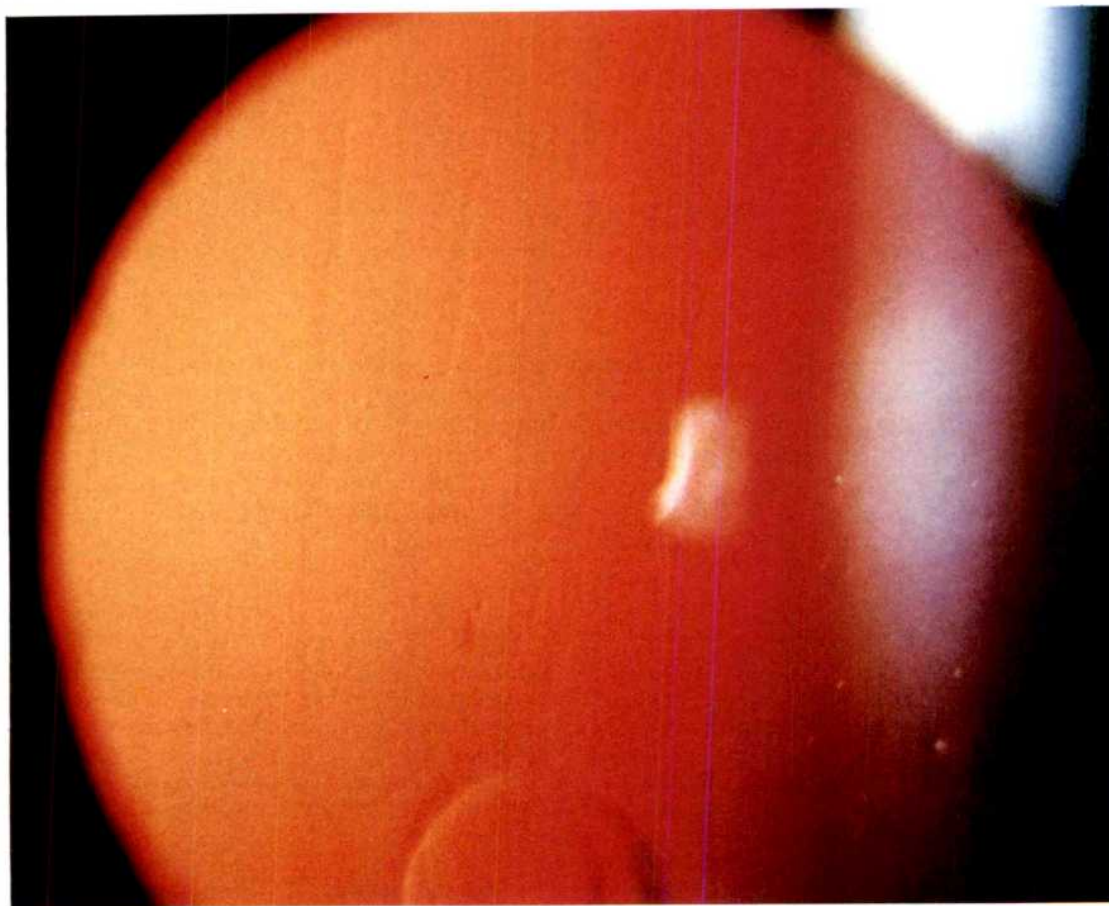


Fig. 1 Corneal oedema produced by having the subject wear a 0.5 mm thick HEMA lens for three hours (open eye). Corneal striae are present. The inferior round area that appears elevated is a large dimple caused by a trapped air bubble between the lens and cornea.

power of -2.00 D, total diameter of 13.5 mm, and thickness of 0.2 mm and 0.5 mm. The 0.2 mm thick lens was worn in the closed eye and the 0.5 mm thick lens was worn in the open eye for three hours to show whether the striae were repeatable with different levels of hypoxia.

PHOTOGRAPHY

To achieve good slit-lamp photography of the striate lines the pupils were widely dilated, so that a wide area of the cornea could be photographed. The two methods used were direct focal illumination¹⁰ and retroillumination from the fundus. The retroillumination method utilised an intense vertical parallelepiped beam, placed just inside the widely dilated pupil margin, thus illuminating the cornea by retroillumination from the fundus.

An adapter that allowed photography through the optical system of a Haag-Streit model 900 slit-lamp was used for the project. The camera body was a Nikon FE with an all ground glass focusing screen. The camera body was mounted to the slit-lamp eye piece with the adapter so that alignment and focusing were possible through the camera viewfinder. The camera was set on the automatic mode for the photography, and exposure time was thus determined by the camera's built-in meter.

The film used was Kodak Ektachrome (ISO 160) balanced for tungsten illumination.

The linear magnification produced by this system of photography was either $2.2\times$ or $3.4\times$ for all shots.

EXPERIMENTAL DESIGN AND PROCEDURE

The corneal swelling responses to the physiological



Fig. 2 Corneal oedema produced by having same subject as in Fig. 1 wear a 0.2 mm thick HEMA lens for three hours (closed eye). Corneal striae are present. Note that the location and configuration of these lines are the same as in Fig. 1.

stress of hypoxia created by the thick hydrogel lenses were determined by having each subject wear low water contact lenses (38.6%) for three hours.

Three separate sessions of photography were held. During one the undisturbed cornea was photographed, and during the second and third the cornea was photographed after (a) three hours of 0.5 mm thick lens wear (open eye) and (b) three hours of 0.2 mm thick lens wear (closed eye) respectively.

For the closed eye condition each subject wore a Coverlet adhesive eye occluder (Elastoplast-Beiersdorf, Inc., Conn) over the eye with the contact lens; it was positioned to eliminate any undue pressure on the globe while the eye was kept closed. No more than one lens was worn in any one day. After two and one-half hours of wear the lenses were removed for pupillary dilatation. The lenses were reinserted five minutes after instillation of a mydri-

atic for completion of the three-hour period. The drug was instilled at this time to ensure mydriasis, because an earlier pilot study had shown that instillation of the drug prior to lens wear did not ensure effective mydriasis after three hours.

To enable entoptic observation of the striae the illuminating arm of the slit-lamp was placed at an angle of 45° to 50° to the microscope with the beam intensity increased to its maximum. The subjects were then asked to describe the appearance of the striae lines and to remember their configurations. A careful slit-lamp examination of the cornea was then performed to determine the plane of the striae.

Results

Our results are photographically summarised in Figs. 1 and 2. We noted that the location and configura-

tions of these lines were the same within each subject but different between subjects. In most instances, but only when the beam intensity of the slit-lamp was increased to its maximum, did subjects report entoptic imagery of the striae. On examination, the configuration of the striae matched that of the subjects' description. To the subject they appeared as long or short, thin, greyish lines traversing the cornea. One subject might report three wavy lines or another five straight lines, but, while they varied between subjects, their configurations were always the same within a subject.

Discussion

Examples of entoptic phenomena of corneal origin have been reported.¹³⁻¹⁶ These observations were of a 'groove pattern' formed by the superficial cornea or emanating from defects such as scarring of the corneal surface.¹⁷⁻¹⁹

This study reports that corneal striae are repeatable both in location and in configuration (after being induced by thick HEMA lenses) in the normal adult cornea, and that they are entoptically visible. The vertical or near-vertical striae were determined by slit-lamp examination to be in the deep stroma and Descemet's membrane. Endothelial folds were not observed. The collagen fibril in the posterior stroma is, as stated by Tripathi²⁰ from histological evidence, to vary in diameter from 19 to 34 nm while Brown²¹ and later Sturrock⁶ estimated from photomacrographic methods that deep stromal striae seen in normal cornea were in the order of 18 to 22 nm in diameter. Thus there is close agreement between measurements taken from human cadaver specimens examined histologically with those seen and measured by optical methods. Sturrock's work⁶ on the normal non-oedematous cornea indicates that striae are seen adjacent to Descemet's membrane and best sighted by oblique illumination in the marginal zones of the cornea. In addition he found that the incidence of these striae lines was 85% in a series of 200 patients aged between 15 and 96 years. However, we could not detect striae in the undisturbed cornea.

The central deep striae appear to be visualisations of the collagen fibril, which is of higher refractive index than its surrounds, so that the fibrils become more visible entoptically. In addition these striae lines having a diameter of 18 to 22 μm ⁶ are very thin, resulting in light being scattered once it has traversed the cornea, which is then seen entoptically.

Are corneal striae lines 'fingerprints', or more appropriately 'cornea stromal prints'? Evidence from this study appear to suggest that indeed they may very well be. All subjects seen with striae had

different configurations and locations of these lines when carefully examined. The phenomenon of entoptic visualisation of striae in contact lens wearers reported by the patient should alert the clinician to the possible cause of them, namely, corneal oedema.

The reproducibility and entoptic phenomena of corneal striae lines lead one to suggest that the healthy, avascular, transparent cornea has certain localised areas in its anatomical structure which are susceptible, and therefore, may give rise to bundles of collagen fibres being visible objectively and subjectively during conditions of corneal swelling. The entoptic phenomenon appears to result from a scattering of light from these striae lines when the light beam is increased to its maximum intensity.

Since the striae appear by slit-lamp visualisation to be deep, the mechanism is thought to be due to laking of fluid separating the collagen fibres. Their appearance is therefore the exhibition of an anatomical arrangement of the fibres at the very early stages of stromal oedema due to endothelial dysfunction.

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Two laboratory methods for diagnosis of herpes simplex keratitis

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SUMMARY Two techniques are described which enable a rapid diagnosis of herpes simplex keratitis to be made. The tests, antibody/antigen reactions, were shown to be accurate and sensitive in the 119 patients examined. A result is available within four hours with the indirect peroxidase-antiperoxidase method and within one hour with the direct method. The techniques are relatively inexpensive, though labour intensive. Negative reactions were found in treated cases and in those with some delay in the histochemical staining.

In many cases of herpes simplex keratitis the clinical findings are pathognomonic, and there is little doubt about the diagnosis. There are a number of situations, however, where one may suspect herpes simplex virus to be the causative factor when the picture is not typical.¹ These patients present a diagnostic problem, and the danger is that they will be started on therapy which may be inappropriate and possibly toxic to an already damaged cornea. In addition, such treatment may so confuse the clinical picture that a correct diagnosis is impossible at a later date. Such cases require, therefore, a laboratory diagnosis.

Various techniques are used to establish a diagnosis of herpes simplex virus infection. Culture tests for virus isolation²⁻⁴ produce a variable yield,^{3,4} and the technique is difficult and time consuming, requiring two to five days. Serological examination⁵ provides, at best, confirmatory evidence, and in addition a high antibody titre is not normally achieved, for up to 90% of the population have a low titre owing to previous infection.⁶ Direct demonstration of the agent in exfoliated cells⁷ is generally less sensitive than cell culture; the smears must be of high quality and the virus inclusions are difficult to detect. The measurement of tear antibodies may be helpful but is time consuming.² Electron microscopy of cells taken from infected tissue is accurate,⁸ but the procedure is expensive, slow, and of limited clinical value.

We describe two immunocytochemical tests which are rapid, simple, and reasonably inexpensive.

Patients and methods

One hundred and nineteen patients were examined to assess the accuracy, predictability, and usefulness of the tests.

The initial technique used was the indirect peroxidase-antiperoxidase (PAP) corneal smear method, with which we examined 58 patients over the age of 10. During a six-month period patients who presented with herpetic corneal lesions, both treated and untreated, and corneal ulcers of doubtful aetiology were investigated. On presentation to the External Eye Disease Clinic scrapings were made from the epithelial lesions by one of the three clinicians involved. Amethocaine topical anaesthesia was used, and under microscopic control the tissue was removed with a Bard-Parker blade. Great care was taken to ensure that an adequate amount of material was obtained and that it was spread evenly on the slides. Two smears were obtained from each patient, one being used as a control. The eye was padded for 24 hours following the procedure. The slides were transported to the laboratory for immediate testing.

In the second part of the study we examined 61 patients with the same inclusion criteria as the first group. Smears were taken in a similar manner, but the direct immunoperoxidase method was used instead.

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LABORATORY METHODS

Smears were made on perfectly clean slides by a streaking technique to achieve separated and flattened cells. This area was outlined with a diamond pencil and smears were then fixed in acetone or Cytofix for five minutes. They should be stained as soon as possible after receipt in the laboratory.

PAP TECHNIQUE

The endogenous peroxidase was removed by treating smears in 3% H_2O_2 (100 vols) in methanol for 20 minutes. The slides were gently rinsed with trometamol (TRIS) saline, pH 7.6, and left standing in this for five minutes. The excess liquid was carefully wiped away from around the smear area. Four to 6 drops of normal swine serum diluted 1/10 in trometamol buffer, pH 7.6, were then applied and incubated for 20 minutes. The serum was then tapped off and the excess wiped away. Four to 6 drops of rabbit antibody to herpes simplex virus type 1, diluted 1/250 in trometamol buffer were applied, and incubated for 20 minutes. The slides were washed gently about six times in trometamol saline and left standing in the final rinse for five minutes. The excess liquid from around the smear was wiped away. Four to six drops of swine antibody to rabbit immunoglobulin diluted 1/100 were applied. The slides were gently washed well with trometamol saline, and left standing for five minutes in the final rinse before excess liquid was wiped away. Four to 6 drops of the PAP complex diluted 1/100 were added, and the slides were then incubated for 20 minutes before being washed well with trometamol saline.

All sera reactions were carried out in a humidity chamber at approximately 30°C. The substrate solutions used to give the coloured results for interpretation were as follows.

(1) *Diaminobenzidine tetrahydrochloride (DAB)* was used in 30 cases. This was prepared immediately before use by dissolving 6 mg of 3,3-diaminobenzidine tetrahydrochloride in 10 ml of 0.05 M trometamol buffer, pH 7.6, with the addition of 0.1 ml of 3% H_2O_2 (100 vols). The solution was filtered if precipitation occurred. The application time was five minutes at room temperature. After the application of DAB substrate 4 to 6 drops were placed on each smear. The slides were then rinsed with distilled water, counterstained with Mayer's haematoxylin for three minutes, and blued in running water for five minutes, dehydrated, cleared, and mounted in synthetic resin.

(2) *Aminoethylcarbazole (AEC)*¹⁰ was used in 28 cases. 4 mg of 3-amino-9-ethylcarbazole was dissolved in 1 ml N,N dimethylformamide and added to 14 ml of 0.1 M acetate buffer, pH 5.2. 0.15 ml of 3% H_2O_2 (100 vols) was added, and this was then

filtered on to the slides. The application time was 45 minutes at room temperature. Slides were then counterstained with Mayer's haematoxylin and hydromounted.

The controls for the substrates were fresh normal blood films fixed in ethyl alcohol and 10% formalin. The positive control used was a tissue section infected with herpes simplex virus, and the negative control was a duplicate corneal smear substituting non-immune rabbit serum for rabbit antibody serum.

RAPID DIRECT METHOD FOR CORNEAL SMEARS

The smears were made and fixed as in the PAP technique. They were then treated with 3% H_2O_2 in methanol for five minutes. The slides were washed gently with distilled water and finally with trometamol saline and left standing in it for five minutes. Excess liquid was carefully wiped away from around the smear area. Four to 6 drops of a protein blocking agent (0.1% bovine albumin, 0.1% immunoglobulin, 0.1% gelatin in 0.05 M trometamol buffer, 15 mM sodium azide as preservative) were added and left for five minutes. Excess liquid was wiped away. Four to 6 drops of peroxidase conjugated rabbit immunoglobulin were added to human herpes simplex virus type 1 diluted 1/50 in trometamol buffer, pH 7.6, and left for 20 minutes. The slides were then washed well with distilled water and treated with the aminoethylcarbazole substrate for 30 minutes. They were then washed well with distilled water and stained with Mayer's haematoxylin for three minutes, blued in running water for five minutes, and mounted in glycerol gel.

The control for the AEC substrate was a fresh normal blood film fixed in ethyl alcohol and 10% formalin. The negative control used was a duplicate corneal smear treated similarly as the test smear, substituting rabbit immunoglobulin in herpes simplex virus negative serum for the peroxidase conjugated sera.

Results

No clinical information was given to the pathologist and only at the end of the study was the clinico-pathological correlation made. Fifty-eight smears

Table 1 PAP method

	Number	Results
Patients	58	
Definite dendritic ulcers (untreated)	36	All positive
Definite dendritic ulcers (treated)	9	All negative
Controls (1 abrasion, 1 herpes zoster ophthalmicus, 5 bacterial ulcers, 6 with delay in processing)	13	All negative

Table 2 *Direct method*

	Number	Results
Patients	61	
Definite dendritic ulcers (untreated)	29	All positive
Definite dendritic ulcers (treated)	18	All negative
Controls (6 abrasions, 7 bacterial ulcers, 1 delay in processing)	14	All negative

were examined by the PAP method (Table 1) and 61 by the rapid direct method (Table 2).

The preparations examined by the DAB method gave the typical distinct yellow to brownish reaction in the cells containing antigen. Haematoxylin was the counterstain, and the negative cells stained in the conventional way with it. The staining, when the method is executed properly, was never equivocal. Occasional weak non-specific staining was present but this was easily interpreted with experience. AEC positively reacting cells containing herpes simplex virus type 1 antigen gave a clear orange tone in the cytoplasm (Fig. 1), and again negative cells stained only with haematoxylin. Non-specific staining was not found.

All patients with untreated dendritic keratitis had a positive result both by the PAP method and the direct corneal smear method.

A total of 27 patients were on antiviral therapy when corneal scrapings were done. The duration of therapy ranged from one to 14 days. The results were negative in all patients by both methods.

For technical reasons there was a delay in processing of the material taken from seven patients. The time interval was six days to 25 days. All of these specimens were unsatisfactory and autolysis was noted.

Twenty patients were clearly clinically non-herpetic. In all of these the test was negative, as expected.



Fig. 1 Corneal epithelial cells showing strong immunoreactivity for HSV 1 in cytoplasm and nuclei. PAP with ethylaminocarbazole.

Discussion

In a preliminary report on a small number of patients we suggested that an antibody/antigen histochemical test might be useful in establishing an early diagnosis in herpes simplex virus keratitis.¹¹ This larger series confirms our initial impression that it is an accurate, reliable and useful test (method 1). A similar method was reported in assessing a tear film aspirate in a patient with a dendritic ulcer.¹² We have recently modified the technique whereby a result is obtained within one hour (method 2).

All corneal smears taken from patients with dendritic ulcers on antiviral therapy (duration one to 10 days) were negative by the indirect PAP and direct methods. This is of some interest, as it suggests that, while there is still some ulceration present, the antiviral agent had neutralised the virus antigen.

The 20 controls had negative results in all cases. This, coupled with the fact that all the untreated dendritic ulcers gave a positive result, suggests that the tests are reliable and can be used diagnostically in corneal ulceration.

In seven patients the unscheduled delay of more than three days in processing and examining the specimens produced interesting results. In all cases the material proved unsuitable and the results were negative. Slides can be stored at 2–4°C in a trometamol buffer bath, pH 7.6, for up to three days, and other methods of storage are being studied. It was found that no antibody/antigen staining took place after that time, and that the cells appeared morphologically to disintegrate. Either acetone or Cytofix was suitable for fixation and did not interfere with the reaction. Technical accuracy in performing these tests is essential for reproducibility.

From the clinical point of view the corneal scrapings must be carefully taken. There is no ethical problem in doing this, as one of the recognised methods of treatment of epithelial disease of the cornea is debridement.¹³ The material must be spread very thinly and evenly on the slide in order to get the best results. If the material is thickly spread, clumping of the cells occurs, and it is difficult for the pathologist to process and interpret the results. The technique should be strictly adhered to, and carried out precisely, in order to produce the best specimens for examination.

We suggest, therefore, that the tests described above provide a reliable, rapid, and inexpensive method of assessing corneal ulceration and can be used as one of the investigations to establish a positive diagnosis in corneal ulceration. Comparisons were not made with other laboratory techniques such as cell culture or immunofluorescence staining, as it was considered that the

controls (25 in number) sufficiently supported the hypothesis regarding the reliability and specificity of the techniques described.

We acknowledge the secretarial assistance of Mrs Carol Winterbotham.

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Serious eye injury in badminton players

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SUMMARY Serious eye injury can occur in badminton players and may become more frequent. The causes and nature of such injuries in this sport in six patients are discussed. All were playing competitive doubles matches. Penetrating eye injury due to a shattered glass spectacle lens occurred. Players should be advised not to wear spectacles with glass lenses. Ocular protection in this sport is desirable, and the forward player should hold the racket in front of the face.

The ophthalmologist's role in reporting the hazards to the eye in various sports is increasingly important.¹ Ocular injuries in ice hockey and squash have generated a considerable literature and preventive measures have been advised in those games.²⁻⁵ Eye injuries in badminton have been reported by Chandran in Malaysia,⁶⁻⁷ with a peak during the 1970 Thomas Cup. Blonstein,⁸ who has been associated with squash and badminton sports medicine since 1946, reported that 'on the whole serious eye injuries are extremely rare in badminton'.

Six serious eye injuries from badminton play are reported here in the hope of encouraging better ocular protection in this popular sport.

Subjects and methods

Six patients with eye injuries from playing badminton were examined by the author at the Leicester Royal Infirmary. All were local amateur players. One other patient, who sustained an injury in India from a shuttlecock causing retinal detachment, is not included, though he was treated in this hospital. Four patients sustained their injuries in 1985 and were seen in the acute phase. Case 3 sustained injury in 1982, case 6 in 1979; both still require outpatient treatment.

Results

Table 1 gives the age, sex, nature of ocular injury, and most recent visual acuity. Table 2 records the details of play when injury occurred. Three patients needed surgery; the others have been treated con-

servatively. All were experienced players, playing doubles at a competitive level. Only case 1 wore spectacles. All had at least 6/6 Snellen corrected vision in the uninvolved eye.

Table 1. Clinical details of patients

Case	Age, sex	Eye	Injury	Most recent VA
1	35 M	L	Corneoscleral perforation, uveal prolapse, glass intraocular FB	6/9
2	61 F	L	Hyphaema, sphincter pupillae tear	6/9
3	20 F	R	Retinal dialysis and detachment	6/9
4	16 M	R	Hyphaema, choroidal rupture involving macula	CF
5	30 M	R	Angle recession glaucoma, vitreous haemorrhage	LP
6	56 M	R	Hyphaema, angle recession glaucoma, optic atrophy	6/9

FB=foreign body. CF=counting fingers at 0.3 m. LP=perception of light only.

Table 2 Sports injury details

Case	Injury	No of years playing badminton
1	Partner's racket broke player's glass spectacles	30
2	Hit by opponent's shuttlecock, smash stroke at net	40
3	Hit by opponent's shuttlecock, smash stroke at net	6
4	Hit by opponent's shuttlecock, smash stroke at net	5
5	Hit by partner's shuttlecock, smash stroke while turning to face him	12
6	Hit by opponent's shuttlecock, smash stroke at net	20

All players were playing competitive doubles matches.

Discussion

Badminton results in few injuries, mostly minor, such as cramps, blisters, and sprains.⁹ Only 6% of all injuries are due to the shuttlecock and 7% to the racket.⁹ These rarer direct injuries are often to the eye and may be severe, as shown in this series. Serious ocular injury is recognised in ice hockey,² squash rackets,³⁻⁵ tennis,¹⁰ and golf,¹¹ but no previous report of perforating eye injury in badminton was found in the literature. Badminton is a very popular sport and often played in schools. The vision in case 4, a schoolboy aged 16, is permanently and severely reduced.

None of these players wore eye protection. Case 1, who was wearing spectacles with glass lenses, was under the false impression that they provided some protection. Had he been wearing toughened, plastic lenses when hit he might have been spared such serious injury. Four patients were injured while close to the net by a shuttlecock from the opponent's smash hit. This type of injury also occurs in tennis players who 'rush the net'.¹⁰ Badminton players and coaches should be aware of this risk in aggressive doubles competitions. The forward player should hold the racket in front of the face while awaiting the return stroke, particularly if a high lob has been delivered, when a smash return is probable. Eye and facial injuries from the shuttlecock may thus be prevented.

Ocular injury rates requiring outpatient treatment in the Southampton study from shuttlecocks were in fact higher than the squash ball injury rates. Severe injuries requiring inpatient treatment occurred there more often from squash.⁴ Badminton players can now achieve greater shuttlecock velocities by using steel framed rackets with carbon fibre shafts than previously possible with the older wooden rackets according to a former badminton coach (Warner J, personal communication). Given these advances in racket technology and a higher outpatient injury

ratio, it is probable that more cases of serious eye injury will occur in this sport. This small cluster of six serious eye injuries in this hospital from badminton may signify a trend if players continue to play without protecting their eyes.

Vinger recommends that all racket players wear eye protection and describes the appropriate products available.¹ Unocular players should be especially mindful of this advice. In addition, prescribers of spectacles should advise badminton players to wear toughened plastic lenses in sturdy spectacle frames. A shattered glass spectacle lens in sport causing serious eye injury may have possible medicolegal implications to the spectacle prescriber as well as being a preventable cause of blindness.

I acknowledge with gratitude the advice given to me by badminton players. I thank the consultants at the Leicester Royal Infirmary for allowing me to report on patients under their care.

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Intraocular reticulum cell sarcoma: diagnosis by choroidal biopsy

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SUMMARY A patient with uveitis and retinal pigment epithelial detachments underwent an extensive medical examination and pars plana vitrectomy in an attempt to confirm the clinical diagnosis of reticulum cell sarcoma. None of these examinations revealed the presence of malignancy. Transscleral biopsy of subretinal lesions confirmed the histopathological diagnosis of reticulum cell sarcoma. The patient was begun on systemic chemotherapy and external beam radiation to the eye and orbit, with resultant preservation of the eye, vision, and probable extension of life because of early detection of reticulum cell sarcoma by choroidal biopsy. This technique may be advantageous in the diagnosis cases of eyes with clinical evidence of reticulum cell sarcoma, no systemic signs of malignancy, and negative vitreous biopsies.

Reticulum cell sarcoma is a highly malignant multicentric form of non-Hodgkin's lymphoma that may primarily affect the eye and central nervous system. Intraocular involvement typically presents as a picture of unilateral or bilateral chronic posterior uveitis that is poorly responsive to systemic corticosteroid or antimetabolite therapy.

Gass and colleagues¹ have described the presence of multifocal solid pigment epithelial detachments to be virtually pathognomonic for reticulum cell sarcoma. Ocular findings may precede central nervous system involvement by months or even several years. Patients with reticulum cell sarcoma are typically 40 years of age or older. Confirmation of the diagnosis of ocular reticulum cell sarcoma has traditionally been based on histopathological study of post-mortem eyes, enucleated eyes, or vitreous specimens. Michels and colleagues² reported two cases in which the diagnosis of reticulum cell sarcoma was made on vitreous aspirate obtained by pars plana vitrectomy. Peyman and colleagues³ reported a case in which the diagnosis was made by full thickness eye wall biopsy.

Establishing the diagnosis of intraocular reticulum

cell sarcoma is important with respect to treatment of ocular complications and recognition of systemic disease. Since the central nervous system is commonly affected by this tumour, computerised tomography and other diagnostic methods are indicated. Early diagnosis is important, because both ocular and central nervous system reticulum cell sarcomas are highly sensitive to irradiation, which may preserve visual function and prolong life.

Recent reports have emphasised the importance of vitreous biopsy in diagnosing chronic cellular infiltration of the vitreous in reticulum cell sarcoma.^{2,4} We here report a case in which the vitreous biopsy was negative, and the diagnosis of ocular reticulum cell sarcoma was made by transscleral choroidal biopsy.

Case report

A 67-year-old woman presented with a one-year history of vitreous floaters and decreased vision involving the right eye. In April 1985 she was treated with cryopexy for a retinal tear in the right eye. No other ocular abnormality was noted at that time. Two weeks after cryopexy, vision in the right eye decreased further. Examination at this time revealed elevated retinal lesions in the posterior pole and visual acuity of 20/100 in the right eye. A presumptive diagnosis of chorioretinitis was made. Clindamycin therapy was begun and a single corticosteroid injection

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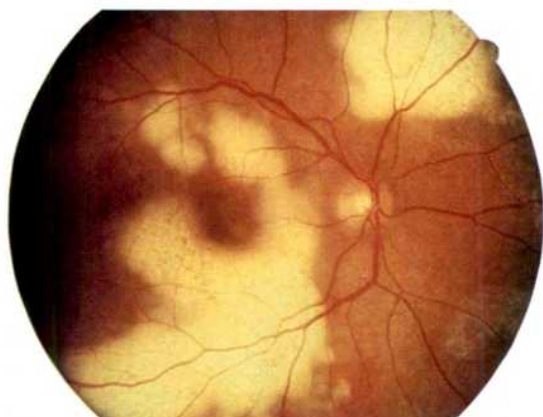


Fig. 1 Fundus photograph of the right eye showing multiple subretinal lesions in the posterior pole.

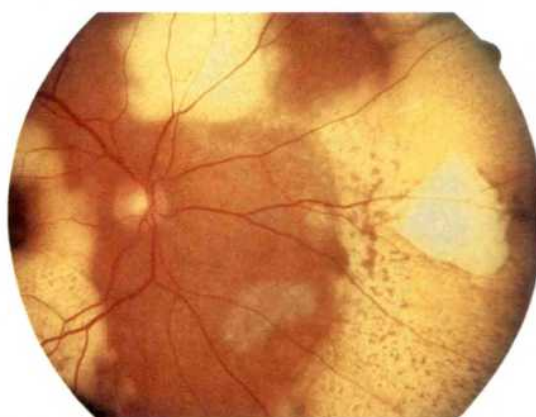


Fig. 2 Fundus photograph of the right eye showing lesions in the nasal periphery.

tion was given transconjunctivally beneath Tenon's capsule. After this therapy the vision improved to 20/60, but two weeks later additional large posterior lesions, as well as many satellite subretinal lesions, were noted in the posterior pole (Figs. 1, 2).

An investigation for reticulum cell sarcoma was performed. General physical examination, neurological testing, breast examination, computerised tomography of the head, and chest x-ray were normal. The white cell count, blood chemistry, antinuclear antibody test, erythrocyte sedimentation rate, fluoresceinated treponemal antibodies, toxoplasmosis titre, cytomegalic virus titre, and urine analysis were all within normal limits; a purified protein derivative skin test was negative.

The patient's past medical history was significant for hypertension, for which she was being treated with prazosin hydrochloride (Minipress) 1 mg three times a day. She had a history of hysterectomy with

bilateral salpingo-oophorectomy for benign fibroids of the uterus and was taking oestrogen (Premarin) 0.625 mg five days per week for menopausal symptoms. Her family history included one brother with hypernephroma.

The patient underwent a diagnostic pars plana vitrectomy of the right eye on 10 June 1985. Cytological preparations revealed a non-specific chronic inflammatory cell infiltration without obvious malignant cells. Ocular examination four days later on referral to the Estelle Doheny Eye Clinic/University of Southern California Department of Ophthalmology showed best corrected visual acuity of 20/100 in the right eye and 20/50 in the left eye; vision in the left eye improved to 20/40 with pinhole. The pupils were 4 mm on both sides and were equally reactive to light; there was no afferent pupillary defect. The results of external examination of the lids, lacrimal glands and lymph nodes were within normal limits.

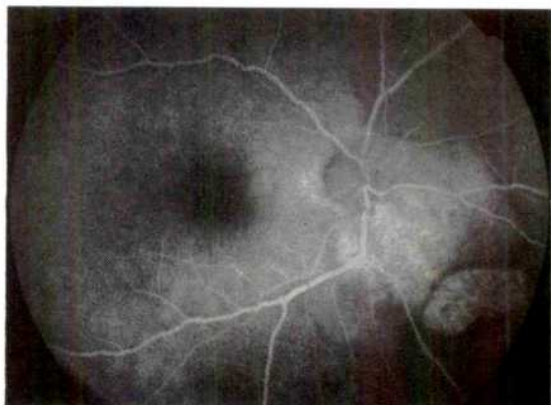
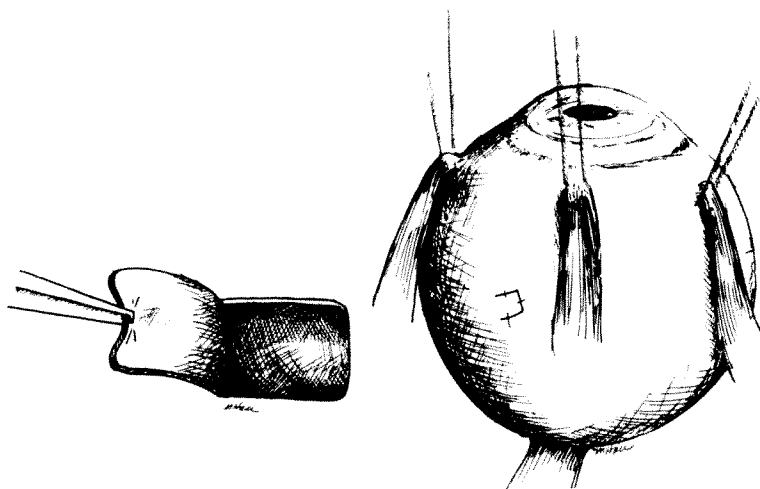


Fig. 3 Arteriovenous phase of the fluorescein angiogram of the right eye showing early blockage of background choroidal vasculature.



Fig. 4 Fluorescein angiogram of right eye showing late staining of the subretinal lesions.

Fig. 5 Diagrammatic representation of the area of choroidal biopsy.



Fine endothelial keratic precipitates with trace flare in the anterior chamber were observed on slit-lamp examination of the right eye. There was no evidence of iris nodules. The lens showed mild nuclear sclerosis, and the vitreous cavity contained a moderate number of cells. Slit-lamp examination of the left eye showed trace cells and flare in the anterior chamber and mild cells in the vitreous cavity.

Fundus examination of the dilated right eye disclosed several raised, lobulated, yellowish, subretinal lesions involving the posterior pole and equatorial region; the peripheral retina appeared normal. Several of these subretinal lesions were interconnected by pigment clumping on their surfaces. Many small satellite lesions were noted. Submacular and perimacular lesions beneath the retinal pigment epithelium were also present. The optic nerve was unremarkable. Fundus examination of the dilated left eye was unremarkable except for a few yellowish drusen-like deposits in the temporal retinal periphery. Ultrasonography of the right eye showed diffuse, highly reflective echoes in the choroid, with shallow serous elevation of the retina and/or pigment epithelium. There was mild to highly reflective thickening of the choroid in the left eye. Ultrasonographic findings were thought to be consistent with metastatic tumours of the choroid. However, ocular reticulum cell sarcoma could not be excluded as a diagnosis.

Fluorescein angiography of the right eye showed diminished background choroidal fluorescence in the vicinity of the lesions with late staining of the lesions (Figs. 3, 4). Fluorescein angiography of the left eye was essentially within normal limits.

The clinical impression was reticulum cell sarcoma involving predominantly the right eye or metastatic carcinoma from either the breast or lung. Repeat physical examination, however, including bone

marrow biopsy, lumbar puncture, computerised tomography of the head, complete blood count, blood chemistry, and liver function tests did not reveal evidence of lymphoma or primary carcinoma. In a further attempt to establish a definitive diagnosis the patient underwent a transscleral choroidal biopsy on 25 July 1985.

Choroidal biopsy was performed under local anaesthesia. The area to be biopsied was marked on the sclera by scleral indentation using indirect ophthalmoscopy. A 2×2 mm full-thickness scleral window was dissected (Figs. 5, 6) and an excisional choroidal biopsy obtained by lifting the choroid through the window with forceps and cutting it free. Clear liquid vitreous fluid drained from the biopsy site in this previously vitrectomised eye. The scleral window was sutured with 9-0 nylon sutures. The vitreous cavity was immediately filled with a 20% sulphur hexafluoride gas/air mixture. Cryopexy was applied to the area of biopsy under indirect ophthalmoscopic control. The retina has remained attached for eight months postoperatively. There have been no apparent complications from this biopsy procedure.

Biopsy yielded four friable fragments of tissue, each measuring approximately 1 mm in greatest dimension. The tissue was fixed in half strength Karnovsky's solution and embedded in paraffin. Sections were cut and stained with either haematoxylin and eosin or periodic acid Schiff reagent. Microscopic examination revealed large round cells with hyperchromatic nuclei and sparse cytoplasm. Admixed with these abnormal subpigment epithelial cells were numerous necrotic cells. The choroid showed diffuse lymphocytic infiltration without abnormal cells. Cytologically the cellular infiltrate in the subretinal pigment epithelial space was consistent with reticulum cell sarcoma (Figs. 6, 7).

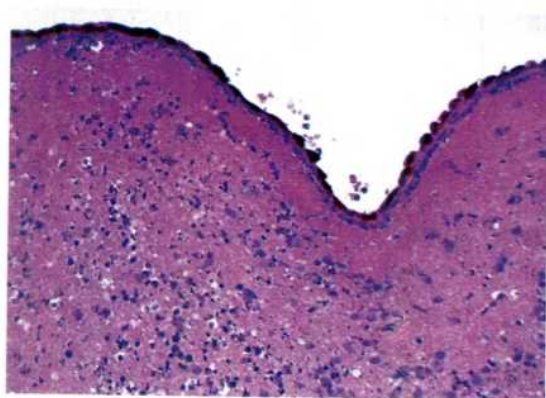


Fig. 6 Subretinal pigment epithelial infiltration by malignant cells. Periodic acid Schiff.

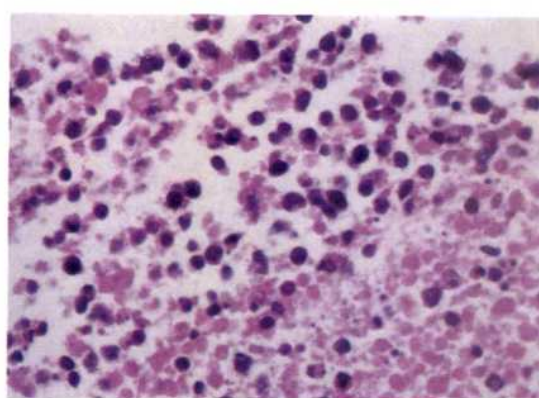


Fig. 7 Biopsy specimen showing malignant cells with scant cytoplasm and large hyperchromatic nuclei. Periodic acid Schiff.

The patient was begun on external beam radiation to the posterior segments and orbits bilaterally. Whole brain and orbital (choroidal) irradiation of 4000 rad was delivered in 180-rad fractions. Parallel-opposed ports of cobalt-60 down to the level of the second cervical vertebra were used. Twenty-two fractions were given over 33 days. Methotrexate was given intrathecally via lumbar puncture in 12 mg doses at weekly intervals for one month for a total of 48 mg. Leucovorin, 25 mg, in six divided doses over 36 hours was given midway through the methotrexate therapy. Within two weeks the best corrected visual acuity had improved to 20/60 in the right eye with partial resolution of the submacular lesions. At eight months the best corrected vision was 20/40 on the right with no evidence of recurrence of the ocular lesions (Fig. 8) and no apparent complications of the choroidal biopsy procedure.

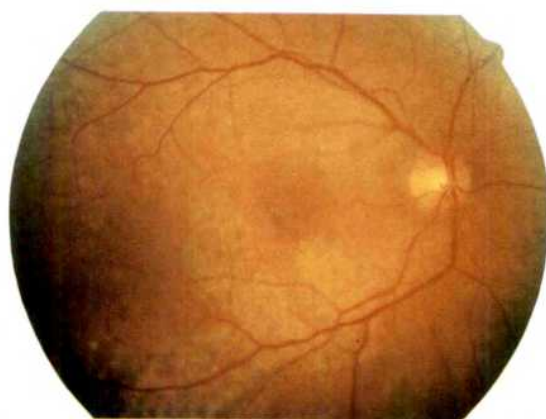


Fig. 8 Fundus photograph eight months after biopsy. Mild mottling of the retinal pigment epithelium is present in areas of previous tumefaction.

Discussion

Ocular reticulum cell sarcoma, whether primary or secondary, is an uncommon but highly malignant form of non-Hodgkin's lymphoma. Numerous cases of orbital and intraocular involvement have been reported.⁵⁻¹⁶ Ocular reticulum cell sarcoma commonly occurs in synchrony with central nervous system involvement.¹⁷ Barr and colleagues¹² reviewed 14 cases of intraocular reticulum cell sarcoma, none of which subsequently showed systemic malignancy; Klingele and Hogan¹³ reported eight cases, of which only one later developed systemic disease. Similar discrepancies in nature and incidence of dissemination are found in other case reports.^{12,14,15} Most authorities consider ocular reticulum cell sarcoma to represent a manifestation of multicentric reticulo-endothelial malignancy. Ocular findings are often among the first to become clinically evident.

Classically, patients with ocular reticulum cell sarcoma present with long standing panuveitis, anterior chamber reaction, decreased visual acuity, vitreous cellular reaction, and refractoriness to therapy. Increased intraocular pressure, keratic precipitates, chorioretinal infiltrates, and serous retinal detachments may also be present. While most cases of intraocular reticulum cell sarcoma affect the posterior segment of the globe, involvement of the iris and ciliary body has also been reported. Vitreous cellular reactions have been described as sometimes resembling primary inflammation, thereby failing to show evidence of intraocular malignancy.¹⁸ Because the central nervous system is frequently affected, computerised tomographic scans and careful neurological examination are strongly recommended. It has been suggested that reticulum cell sarcoma must always be kept in mind whenever patients with chronic idiopathic uveitis present with neurological

symptoms.^{1,6,9,10-13} Biopsy proved cases of reticulum cell sarcoma histopathologically show large hyperchromic cells with sparse cytoplasm, indented nuclei, and prominent nucleoli.

Cytological confirmation of intraocular lesions suspected of being reticulum cell sarcoma is often difficult. Michels *et al.*² and others⁴ have described the use of pars plana vitrectomy to obtain filtered vitreous aspirates in establishing the diagnosis. Peyman and coworkers³ described a case of ocular reticulum cell sarcoma diagnosed by full thickness eye wall biopsy. Brain biopsy has also been proposed as a potential diagnostic approach after negative vitreous biopsy.⁶ Lang and associates⁷ recently described an interesting case which presented as bilateral panuveitis with multifocal, discrete retinal lesions. Pars plana vitrectomy failed to confirm the suspected diagnosis of ocular reticulum cell sarcoma. Three years later, at necropsy, examination revealed reticulum cell sarcoma involving the brain and both eyes.

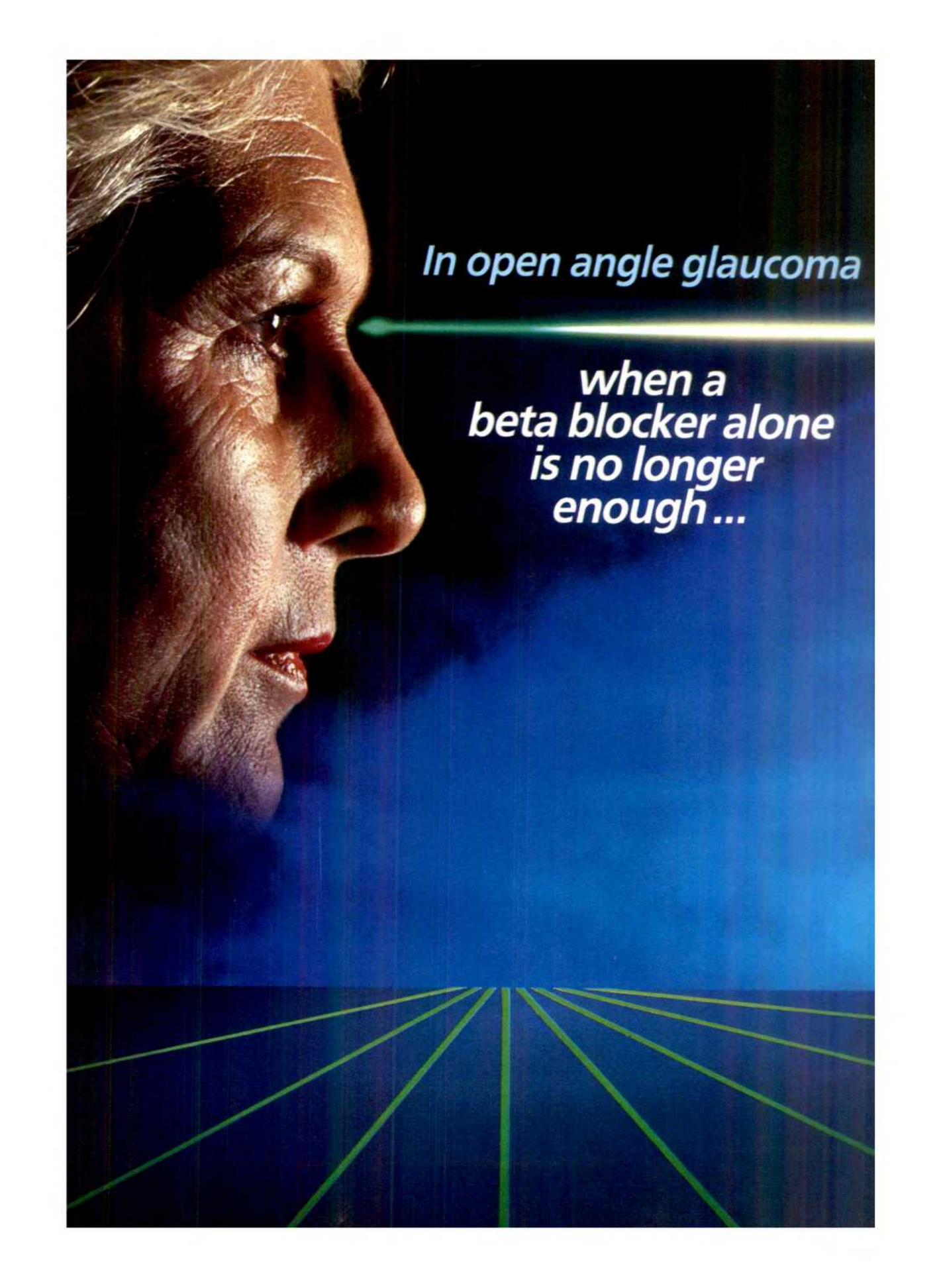
With proper technique it is possible to obtain a biopsy specimen of retina and choroid without significant complications.¹⁹⁻²¹ Potential complications of choroidal biopsy include: intraocular haemorrhage, retinal detachment, choroidal detachment, endophthalmitis, and retinal incarceration into the biopsy site. Transscleral choroidal biopsy offers a promising alternative diagnostic approach to lesions that are clinically suggestive of reticulum cell sarcoma but have yielded negative vitreous biopsies. Because these lesions are often responsive to irradiation and chemotherapy, early diagnosis with prompt therapeutic intervention may contribute to the preservation of visual function and prolongation of life.²⁻⁵ We believe that transscleral biopsy is indicated in patients with negative vitreous biopsy and strong clinical evidence of this life-threatening malignancy.

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Oncocytoma of the eyelid: a case report

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From Moorfields Eye Hospital, High Holborn, London WC1V 7AN

SUMMARY Oncocytic tumours of the eyelids are rare, only one previous case having been reported. This paper describes a second such lid tumour affecting the medial upper lid. We present the clinical features, surgical management, and histology of the lesion.

Oncocytomas are benign adenomatous tumours composed of oncocytes, a name coined by Hamperl.¹ These tumours have also been called oxyphilic adenomas. Oncocytic tumours of the ocular adnexae are rare, such a lesion having first been reported by Radnóti² in 1941. The lesion he described involved the lacrimal sac. The total number of oncocytomas of the ocular adnexae so far reported in the world literature is 34. Of these only one other case involved the eyelid.

We report here a second case of an oncocytoma involving an eyelid.

Case report

A 67-year-old man presented in 1981 with a five-year history of a slowly enlarging right upper eyelid mass. It was reddish in colour, occupied the medial one-third of the lid, and tended to fluctuate in size. The tumour surrounded the upper canaliculus and caused pouting of the punctum but did not involve the caruncle. A biopsy was performed, and the tumour was found to be an oncocytoma. It was treated with radiotherapy (3750 rad in five fractions over three weeks). This produced no noticeable response. The patient was then referred to the Moorfields Oculoplastic Unit for further management. Unfortunately he was also found to have thoracic, abdominal, and femoral aneurysms which required aortofemoral grafting. As this took priority he did not come to us again until 1985. Over the intervening period the tumour had increased by only about 1 mm in size, measuring 6×8 mm in diameter (Fig. 1). It was smooth and of a dark reddish hue, this being more clearly apparent on the subtarsal surface (Figs. 2A, 2B).

The tumour was removed under local anaesthesia as a full-thickness, pentagonal lid resection incorpo-

rating a 2 mm clear skin margin. The upper lacrimal canaliculus was sacrificed in the process, leaving a large defect which comprised almost half the total eyelid length (Fig. 3). A primary closure of the lid defect was achieved by performing an upper limb lateral cantholysis, freeing the orbital septum, and suturing the cut medial end of the remaining tarsal plate to the posterior limb of the medial canthal tendon. The orbicularis muscle and skin were closed directly. This procedure produced a comfortable and cosmetically satisfactory result (Fig. 4). During a follow-up of nine months the patient remained asymptomatic.

HISTOLOGY

Paraffin sections of the specimen showed that the tumour was composed of several lobules and nodules which contained anastomosing cords and islets of eosinophilic cells with glandular spaces and focal ducts filled with eosinophilic debris (Fig. 5). The tumour cells were large, polygonal, and contained abundant granular cytoplasm. The nuclei were rounded or oval, regularly arranged, with prominent



Fig. 1 Oncocytoma of the right upper eyelid, involving the upper lacrimal punctum.



Fig. 2A Skin surface of excised tumour specimen.



Fig. 2B Conjunctival surface of the excised tumour specimen.

nucleoli (Figs. 5, 6). The tumour occupied almost the full thickness of the lid, ulcerating on the conjunctival side and causing attenuation of the overlying epidermis on the skin side. The microscopic features were consistent with the diagnosis of oncocytoma (oxyphilic adenoma).

Discussion

The term oncocytoma refers to tumours composed of large eosinophilic cells (oncocytes) growing in an adenomatous pattern. Oncocytomas are most commonly found in salivary glands but have been described in the thyroid, parathyroid, pituitary and adrenal glands, and also in the kidney, testes, pharynx, larynx, and trachea.

The first mention of oncocytes in the ophthalmic literature was by Böck and Schlagenhauff,¹ who noted their presence in the lacrimal glands of seven out of 20 necropsy cases. Radnóti² reported the first case of an oncocytoma of the ocular adnexae, occurring in the rear sac wall in a 66-year-old woman with chronic dacryocystitis.

The existing literature was reviewed by Biggs and Font³ in 1977 and totalled 17 reported cases of oncocytoma affecting the ocular adnexae. To these they added a further 17 previously unreported cases which were on file at the US Armed Forces Institute of Pathology.

The caruncle is the site of predilection for adnexal oncocytomas, accounting for 56% of reported cases, with the lacrimal sac coming second (24%).



Fig. 3 Right upper lid defect resulting from the tumour excision (and part of the upper lacrimal canaliculus).



Fig. 4 Reconstructed right upper lid four months after excision of oncocytoma.

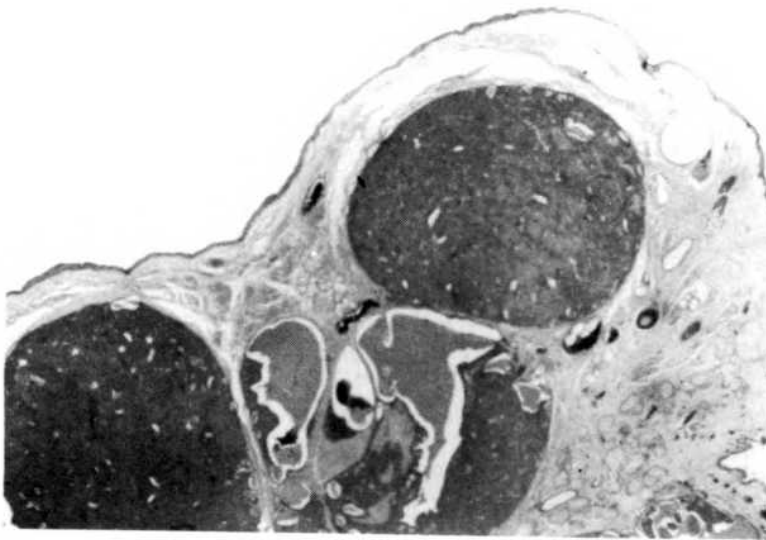


Fig. 5 Oncocytoma of eyelid. Rounded nodules of tumour and adjacent dilated ducts filled with eosinophilic debris, lying in dermis. Haematoxylin and eosin.

Only one case of lid involvement with an oncocytoma has previously been reported, and to this we add our case. The diagnosis was made on biopsy, though the lesion did display the characteristic cherry red colour previously noted in caruncular tumours. This was particularly obvious on the conjunctival surface when the lid was everted. The slow growth and smooth contour are further pointers to the diagnosis. The eyelid as the tumour site does not present any special management problems. Our case did not improve following radiotherapy, and therefore the treatment of choice would appear to be

complete surgical excision with primary repair of the resulting defect, according to the conventional principles of lid closure and reconstruction.

In spite of the frequent occurrence of oncocytes in the lacrimal gland, this is a rare site for oncocytic tumour formation.¹ When they occur they may be malignant, two of the three reported lacrimal gland tumours being oncocytic adenocarcinomas. In general, though, oncocytomas run a slow and benign course.

The origin of oncocytes remains a matter of some debate. They seem to occur in aged individuals,

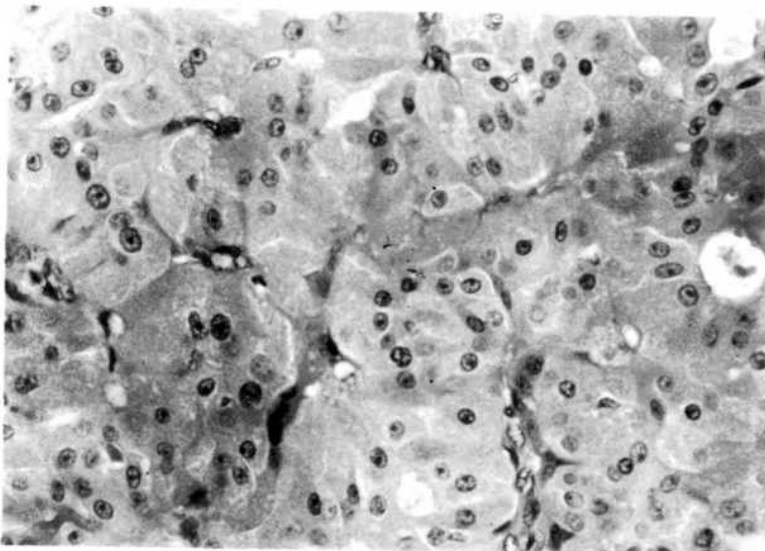


Fig. 6 Oncocytoma of eyelid. Trabecular pattern of tumour, with focal acini consisting of polygonal cells with eosinophilic granular cytoplasm and rounded regular nuclei, with prominent nucleoli. Haematoxylin and eosin.

implying degenerative change, though the cells contain excessive numbers of mitochondria and few other organelles, which would tend to suggest increased cellular metabolism. Radnót resolves this paradox by suggesting that one is dealing with the proliferation of functionally impaired mitochondria, and this contention is supported by the pathological structure of the mitochondria on electron microscopy. Biggs and Font⁴ consider that the lesions which they reported stemmed from oncocytic metaplasia of the ducts and acinar cells of adnexal lacrimal or salivary tissue. Our case may have arisen either from accessory lacrimal gland or from upper lacrimal canalicular tissue.

We thank Mr D S Thompson for kindly referring this case to us.

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Retinal microangiopathy in pigmented paravenous chorioretinal atrophy

SURESH R LIMAYE AND MUNEERA A MAHMOOD

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SUMMARY This report describes an atypical case of pigmented paravenous chorioretinal atrophy, associated with focal progressive peripheral retinal microangiopathy, in a 51-year-old black female. The eyes were asymmetrically involved. Although several cases have been reported with typical features of this uncommon entity, none of them have been known to be associated with retinal microangiopathy. The occurrence of such microangiopathy supports the hypothesis that damage to the retinal photoreceptors may induce retinal microangiopathy, as suggested in other clinical and experimental studies.

Pigmented paravenous chorioretinal atrophy is an asymptomatic disease characterised by the presence of bilaterally symmetrical chorioretinal atrophy along the distribution of the retinal veins with variable pigment migration. The disease progresses slowly and its aetiology remains unknown. As the condition is restricted to the paravenous area, it is thought not to be a sight-threatening generalised degenerative disorder of the retina.¹ Between 1973 and 1980 we examined three patients with pigmented paravenous chorioretinal atrophy, only one of whom had an unusual progressive, peripheral, retinal microangiopathy in the more involved eye. Such a case of retinal microangiopathy has not to our knowledge been previously reported.

Case report

A 51-year-old black female from the West Indies was examined for a routine eye examination in September 1976. She denied symptoms of night blindness or previous ocular disease. Her past medical history was also unremarkable, and there was no family history of night blindness or any other ocular diseases. Visual acuity was 6/6 in each eye. External examination did not reveal any abnormality. Extraocular motility was full, and she was orthophoric for distance and near. Slit-lamp exami-

nation showed only minor cuneiform cataracts in each eye. Intraocular pressure by applanation tonometry was 16 mmHg in each eye.

The fundus of the right eye showed typical paravenous corpuscular pigmentation, with chorioretinal atrophy extending from the optic disc to the equator and beyond (Fig. 1). In the temporal periphery microaneurysms and telangiectasia of the retinal vessel was seen, but without exudates (Fig. 2).

The fundus of the left eye, however, showed only one isolated patch of chorioretinal atrophy along the inferior temporal vein (Fig. 3).

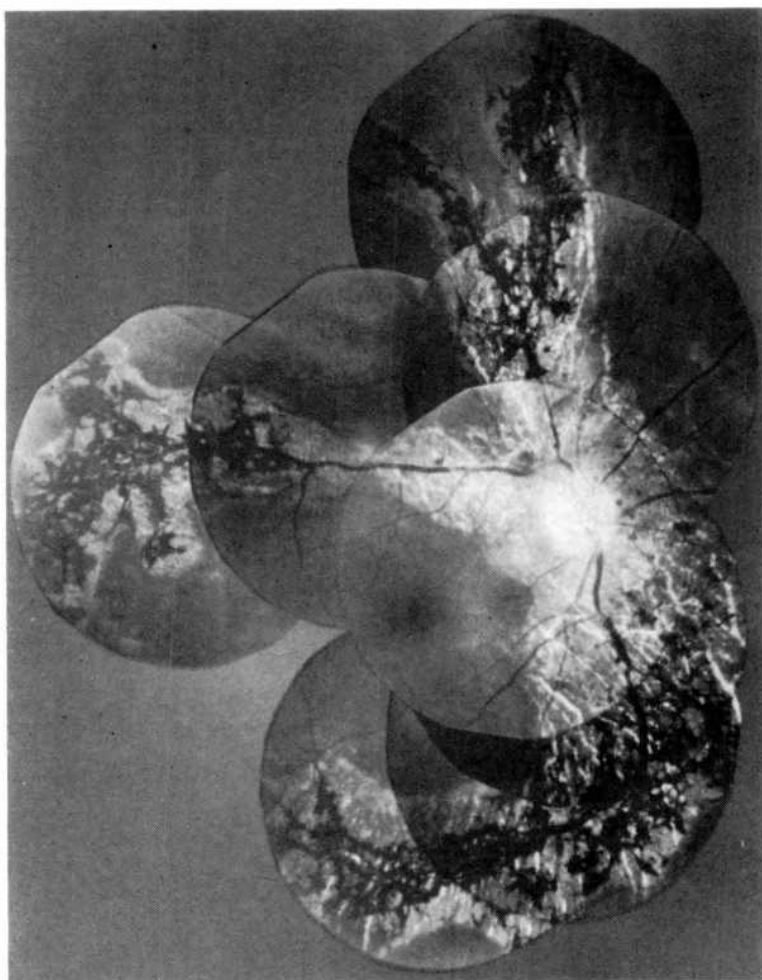
The visual field of the right eye was markedly constricted, especially on the nasal aspect, and that of the left eye was full on Goldmann perimetry (Figs. 4a, 4b). A rod dominant (scotopic) electroretinogram of the right eye revealed subnormal b-wave amplitude (150 μ v) with a normal implicit time (45 m/s). The electroretinogram of the left eye in a rod dominated condition showed a b-wave amplitude of 350 μ v with an implicit time of 45 m/s. Electro-oculography showed the light peak to dark trough ratio of 2.0 for the right eye and 2.3 for the left eye.

Fluorescein angiography of the right eye showed an extensive area of choriocapillaris atrophy with prominently visible choroidal vessels along the major retinal veins adjacent to the disc in an early arterial phase. In the arteriovenous phase hyperfluorescence was seen at the edge of the atrophic area and hypofluorescence was seen corresponding to the areas of pigment migration (Fig. 5).

Systemic examination was unremarkable and

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Fig. 1 Right fundus: a typical paravenous chorioretinal atrophy with pigment migration, and uninvolved macular area.



routine laboratory tests, including serology for syphilis and skin test for tuberculosis, were negative. Haemoglobin electrophoresis did not reveal any abnormal haemoglobinopathy.

Three years after the initial examination she was found to have intraretinal hard exudates in the area of previously noted microaneurysms and telangiectasia, namely, in the temporal periphery of the fundus (Fig. 6). Fluorescein angiography of the peripheral fundus showed areas of capillary non-perfusion, arteriovenous communications, and microaneurysms (Fig. 7).

Discussion

Pigmented paravenous chorioretinal atrophy is an uncommon disease of unknown aetiology. The first case of this disorder was described by Brown in 1937

under the name of retinochoroiditis radiata.² In 1962 Franceschetti coined the term pigmented paravenous choroiditis.³ Several other cases have been published some under different names.⁴⁻⁶ Noble and Carr recently reported six additional cases and reaffirmed its characteristics,¹ previously well described by Krill.⁷ The linear extent of chorioretinal atrophy and paravenous pigmentation is remarkably variable among these cases. A slow progression of the disease without involvement of the macular area has been emphasised.⁵

This case report, however, is unusual because such an asymmetrical involvement is rare, and the presence of retinal microangiopathy has not been described before. As in previously reported cases, there was no evidence of intraocular inflammation, and the laboratory tests for associated systemic disease were negative. The patient also denied

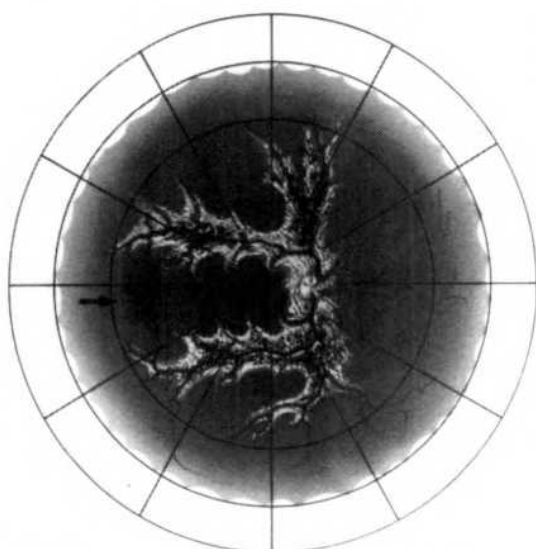


Fig. 2 Microaneurysm and telangiectasia seen in the temporal periphery (arrow) of the right eye.

having a family history of any ocular disorder. At the initial examination only telangiectatic microvascular changes were observed, without any intraretinal exudate. Three years later a collection of hard exudates in the inner retina was observed. Fluorescein angiography in this area showed capillary non-perfusion, arteriovenous communication, microaneurysmal dilatation and vessel wall

staining. A microangiopathy associated with other disorders such as diabetes mellitus, vein occlusion, sickle cell retinopathy, sarcoidosis, Eales' disease, and radiation retinopathy was excluded on the basis of clinical examination and laboratory investigation. Unfortunately not all her family members were available for eye examination, though they claimed to have 'good eyes'.

It is noteworthy that the retinal microangiopathy, though not previously described with pigmented paravenous chorioretinal atrophy, has been noted by Cleary *et al.*⁸ in five cases of congenital hypertrophy of retinal pigment epithelium. Similar retinal vascular abnormalities have been described in rats with hereditary visual cell degeneration,⁹ the light damaged rat retina,¹⁰ and after argon and ruby laser photocoagulation of monkey retina.¹¹ Dantzer and Gerstein¹⁰ observed obliteration of retinal capillaries in cats with iodoacetate induced photoreceptor damage. Telangiectatic changes are known to occur on the optic nerve head in patients with cone-rod degeneration.¹² Therefore it is postulated that in our patient the presence of microangiopathy may signify photoreceptor damage. Whether photoreceptor damage was secondary to primary degeneration of the retinal pigment epithelium is debatable. A marked constriction of the visual field and a sub-normal ERG are, however, indicative of photoreceptor damage. It is not clear why the disease has appeared so asymmetrically. The pathogenesis of pigmented paravenous chorioretinal atrophy by itself and in association with retinal microangiopathy remains unresolved.

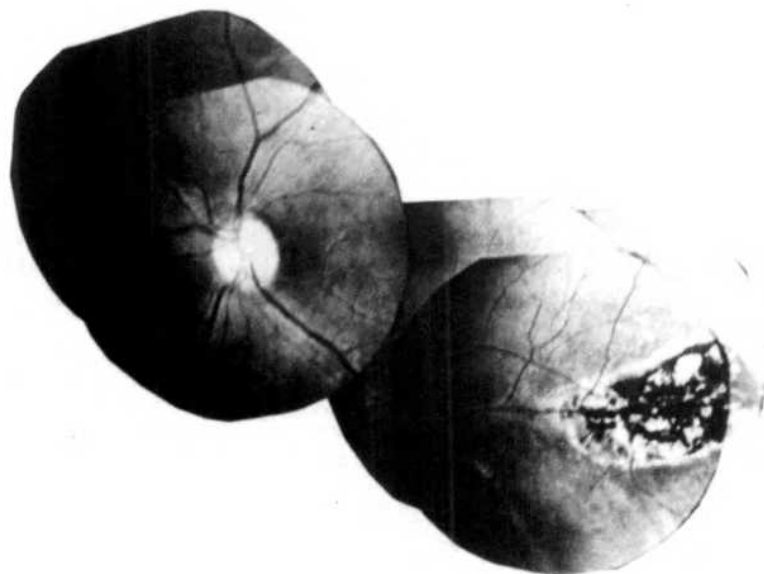


Fig. 3 Left fundus: only an isolated patch of chorioretinal atrophy seen.

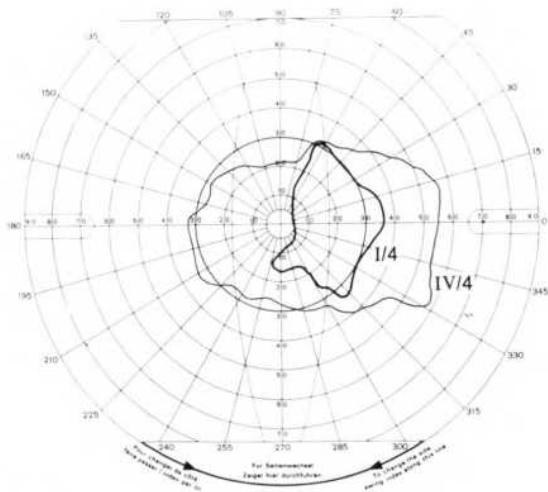


Fig. 4a

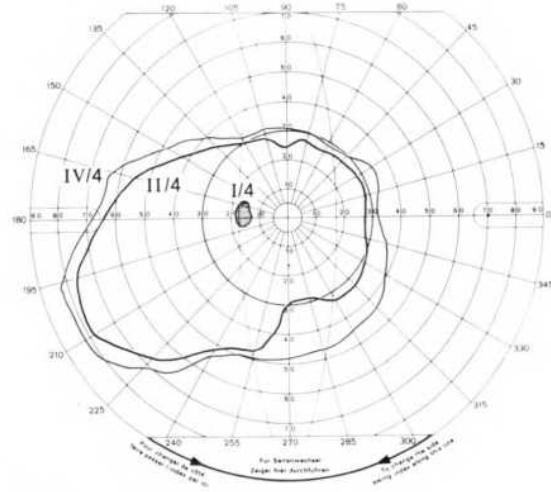


Fig. 4b

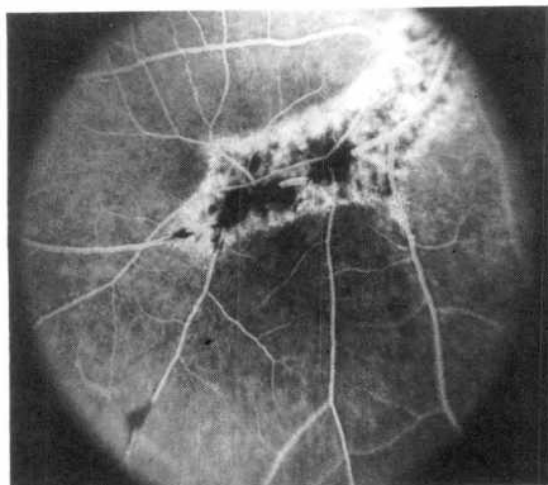


Fig. 5

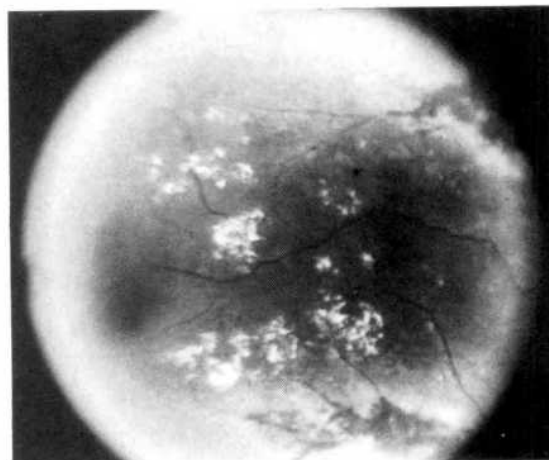


Fig. 6

Fig. 4A Visual field of the right eye.

Fig. 4B Visual field of the left eye.

Fig. 5 Fluorescein angiogram of the right eye showing transmitted hyperfluorescence and blocked fluorescence.

Fig. 6 Temporal periphery of the right eye showing accumulation of hard exudates not seen on the initial examination.

Fig. 7 Fluorescein angiogram of the temporal periphery showing capillary non-perfusion, microaneurysm, and arteriovenous communications.

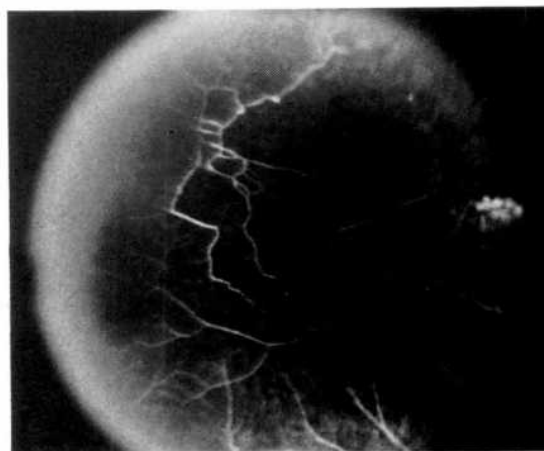


Fig. 7

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Rod-cone interaction in patients with fundus flavimaculatus

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SUMMARY Dark adaptation and the rise of cone flicker threshold (25 Hz) during dark adaptation were measured psychophysically in three patients with fundus flavimaculatus. The dark adaptation curve showed a delayed rod-cone break but a normal final rod threshold in all these patients. However, the rise of cone flicker threshold during dark adaptation was not delayed and also reached a normal final value. This indicates that the delay in rod dark adaptation does not influence the rise of cone flicker threshold during dark adaptation. This finding contrasts with current concepts that the rise of the cone flicker threshold reflects an increasing inhibitory influence of dark adapting rods.

It has been suggested that the rise in cone flicker threshold (CFT) during dark adaptation reflects an inhibitory rod-cone interaction.^{1,2} Usually, the luminance threshold for the detection of flicker has been measured at a constant high temporal frequency (20 Hz or more) in these experiments. At such temporal frequencies the threshold for flicker detection is cone mediated. The CFT was found to be highest under scotopic conditions and lowest when either measured against a large background saturating the rod system³ or immediately after the offset of an intensive bleaching light.⁴ A recent study has shown that the loss of cone flicker sensitivity provided by an inhibitory influence of unstimulated rods goes in parallel with changes in rod absolute threshold across the visual field.⁵

In patients with fundus flavimaculatus, a hereditary retinal disease, dark adaptation is frequently found to be slower than normal when sufficient preadaptation is applied, but final rod thresholds are normal or only slightly elevated.⁶ On the assumption that the rise of CFT during dark adaptation is due to the increasing inhibitory influence of dark adapting rods the rise of CFT should be delayed in patients with fundus flavimaculatus showing a delayed rod-cone break. This was studied in three patients.

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Material and methods

Three patients (two females, 18 and 75 years old, and a male, 30 years old) with retinal lesions typical of fundus flavimaculatus were studied. A detailed description of the clinical findings in these patients is given elsewhere.⁷ During the experiments the subjects' pupils were dilated with tropicamide (Mydriaticum) and phenylephrine (Neo-Synephrine 5%) eye drops. With a Tübinger perimeter dark adaptation and CFT were measured in a similar manner to that outlined by Alexander and Fishman.³ After 10 minutes of intensive light adaptation with a Ganzfeld illumination of 890 cd m⁻² the change in perception threshold was determined for a white circular stimulus with a diameter of 104', presented for 500 ms at a temporal retinal eccentricity of 20°. Foveal fixation was maintained by presenting a deep red central mark. The luminance was increased in steps of 0.1 log units from subthreshold values until the subject responded by means of a buzzer. After renewed identical light adaptation the change in CFT was measured during a second run of dark adaptation. In this case the stimulus flickered with a constant frequency of 25 Hz and the subject was asked to activate the buzzer as soon as flicker became detectable. For each trial the luminance was set below the flicker threshold initially, in order to avoid

flicker adaptation, and then the luminance was increased in 0.1 log unit steps. Threshold was defined as the mean of two repetitions of this procedure.

Results

The rod-cone break in the dark adaptation curve was delayed in all three patients studied. It occurred after 12, 14, and 19 min respectively, whereas the normal range for the rod-cone transition, as determined in more than 20 healthy persons, was from 6 to 10 min after the beginning of dark adaptation under our experimental conditions. There was an apparent positive correlation between the delay in rod-cone transition and the age of the patients, but the number of patients is much too small to tell whether this is of any significance.

The delay of the rod-cone break was most pronounced in patient M (75 yr), known to have fundus flavimaculatus for more than 40 years. In her better, left eye the rod-cone transition occurred during the 19th minute of dark adaptation. The fundus of this eye showed the typical deep-yellowish white retinal deposits of various sizes and shapes in the posterior polar region. Simultaneously she had a macular lesion, most probably senile macular degeneration. Since she had seen much better in her earlier years, a concomitant macular degeneration of Stargardt's type can be regarded as unlikely. She had a small absolute central scotoma in this eye and a visual acuity of 0.2. The ERG and EOG were normal. Her colour vision showed a slight blue-yellow defect, but this might also be due to an early senile cataract.

As shown in Fig. 1 (filled squares), her dark

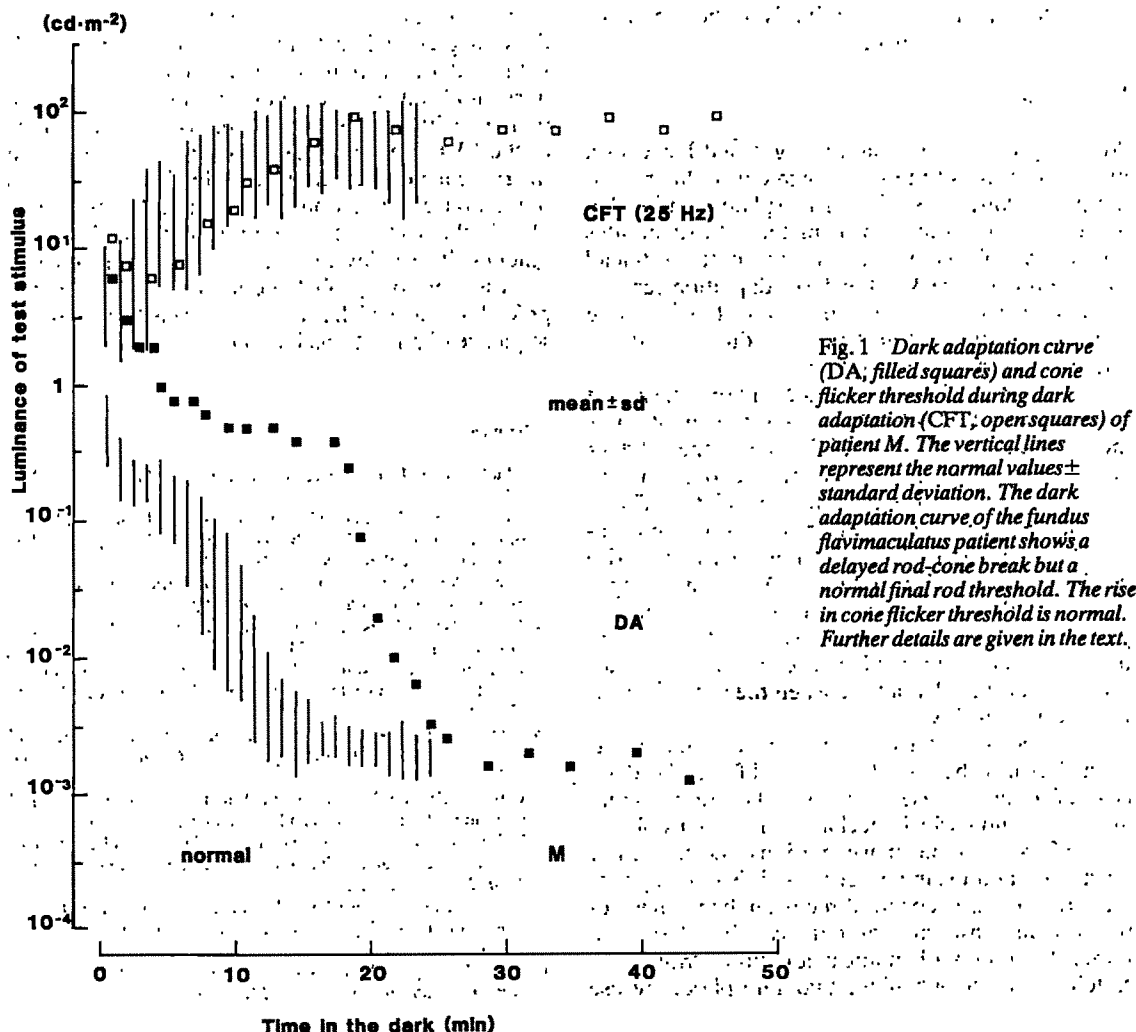


Fig. 1 Dark adaptation curve (DA; filled squares) and cone flicker threshold during dark adaptation (CFT; open squares) of patient M. The vertical lines represent the normal values $\pm$ standard deviation. The dark adaptation curve of the fundus flavimaculatus patient shows a delayed rod-cone break but a normal final rod threshold. The rise in cone flicker threshold is normal. Further details are given in the text.

adaptation curve reached a normal final rod threshold despite the massive delay of her rod-cone transition. The same was true for the other two patients, who also reached normal thresholds after less than 35 minutes of dark adaptation.

Fig. 1 also shows the values for the CFT (open squares) of patient M. After a small initial drop, which is often but not always seen in normal persons too, her CFT showed a completely normal rise. It is especially noteworthy that the CFT had already reached its final threshold, approximately 1.0 log units above the initial value, when the dark adaptation curve showed a rod-cone break.

Similar results were obtained in the two other patients with fundus flavimaculatus. They had a normal time course in the rise of CFT during dark adaptation, although their rod-cone transition during dark adaptation was delayed. Both the final CFT values and the final rod thresholds of these patients were in the normal range.

Discussion

After exposure to an adapting light that bleaches a high percentage of the visual pigments in the retina, peripheral cone thresholds fall to a plateau within 3 to 5 minutes. Only after approximately 8 to 10 minutes does the rapidly increasing sensitivity of the rods lead to the rod-cone break in the dark adaptation curve.^{8,9} In patients with fundus flavimaculatus this rod-cone transition is delayed,⁶ most probably due to a disturbance of rhodopsin regeneration.¹⁰

Bearing in mind the current concept that the rise of cone flicker threshold during dark adaptation is induced by an increasing inhibitory influence of dark adapting rods on cones,¹⁻³ one might expect this rise to be delayed also in fundus flavimaculatus. This is not the case. The three patients with a delayed rod-cone break in fundus flavimaculatus had a normal rise of CFT during dark adaptation. Arden and Hogg¹¹ made a similar observation on a patient with retinitis pigmentosa. This patient had a slowed dark adaptation, and a normal sized increase in the cone flicker threshold occurred at a time when the patient's rods were very insensitive.

Examination of CFT during dark adaptation has been shown to be valuable in the differential diagnosis of retinal disease,¹¹⁻¹³ and it is therefore of great interest to know which mechanism is responsible for the CFT rise under normal conditions. As outlined by Alexander and Fishman⁵ recently, it is unlikely that the threshold rise depends directly on the recovery of rod system sensitivity, as both can be fitted with rather different mathematical equations. Moreover, caffeine and theophylline, two phosphodiesterase

inhibiting drugs, affect the human CFT while leaving dark adaptation unchanged.¹⁴

It has been suggested^{15,16} that the interaction between rods and cones in flicker detection is mediated by a lateral pathway within the outer retina involving horizontal cells. Horizontal cells have been shown to exert a continuous negative feedback on to cones in the dark,^{16,17} and it is known that after a bleach the membrane potential of horizontal cells returns to the resting level well before responses to test flashes re-establish their prebleach amplitudes.¹⁸ Consequently, the electrical signals that mediate this interaction are at least partially independent of the photochemical process of adaptation. If the rod-cone interaction underlying the rise in CFT during dark adaptation occurs via horizontal cells, as is likely,^{15,16} a normal rise in CFT should depend on normal horizontal cell electrical activity. The rod inhibition on CFT is maximal when the rods are completely dark adapted and unstimulated²—that is, when rods with a dark current at its maximum¹⁹ modulate horizontal cell activity. Thus our observation that in patients with fundus flavimaculatus the time course of the CFT rise is normal despite a marked delay in the rod-cone transition suggests that in these patients horizontal cell function is normal and that after a bleach the rod dark current returns with normal kinetics. The delay in regaining normal rod sensitivity is therefore probably due to a disturbance in a preceding stage of the rhodopsin-transducin cascade sequence of phototransduction.

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Epidemiology of intraocular pressure in a population screened for glaucoma*

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SUMMARY This study evaluated the association between intraocular pressure and various sociodemographic characteristics, ocular findings, and cardiovascular risk factors in a population screened for glaucoma. A total of 2594 subjects older than 40 years residing in three urban areas of southern Israel participated. Of those screened 6.1% had a raised intraocular pressure (IOP ≥ 21). The mean IOP increased with age, was higher among persons born in Africa or Asia than those born in Europe or America, higher among myopes than hypermetropes and among those with an enlarged cup-disc ratio (CDR). Analysis of variance tests indicated that refractive status, CDR, age, country of birth, and diabetes were each independently associated with IOP. In addition, associations between raised intraocular pressure and age, country of birth, myopia, CDR, diabetes, and glaucoma in the family were found.

A raised intraocular pressure is a major ophthalmologic risk factor for the development of glaucomatous visual field defects. The prevalence of ocular hypertension is estimated to be between 5 and 10%.¹⁻⁴ Unfortunately the aetiology of this condition and its relationship to glaucoma is not well understood.

This study uses data from the glaucoma screening of a population in southern Israel to investigate the epidemiology of intraocular pressure. Its objectives were to estimate the prevalence of ocular hypertension in the general population and to analyse the relationship of intraocular pressure to various sociodemographic characteristics, ocular findings, and systemic risk factors.

Material and methods

A population screening examination for glaucoma performed between 1982 and 1984 in three urban areas in southern Israel was the source of information for this study. Details of the screening protocol have been published elsewhere.⁵

There were two parts to the examination—an interview and an eye examination—performed at

two stations. On arrival each subject was interviewed by a medical student and the following data were recorded: year of birth, sex, country of birth, systemic illness (diabetes, hypertension requiring current medication, other cardiovascular conditions, and 'other'), history of haemodynamic shock, family history of glaucoma, and description of life style with regard to physical activity. Subjects reporting occasional hypertension, or not receiving medication for it, were not considered as hypertensives for this survey. A subject was considered diabetic if he or she was on a diabetic diet with or without additional regular medications. Cardiovascular conditions (other than hypertension) were heart or peripheral vascular diseases as documented by current medication and/or past admissions to hospital. As to life style, four categories of physical activity were defined as follows: sedentary (e.g., sedentary occupation, no regular physical activity), sedentary with occasional mild physical activity, medium physical activity, and marked physical activity (e.g., strenuous job or housewife, climbs stairs to apartment, etc.). Past haemodynamic shock was recorded when a subject recalled a major operation, accident, or other occasion necessitating blood transfusions.

The eye examinations were carried out by ophthalmologists with at least three years' experience. The parameters recorded were:

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Intraocular pressure (IOP). This was measured with the Goldmann applanation tonometer on either the Haag-Streit 900 or Topcon LD2 slit-lamp. The average of three consecutive readings was recorded for each eye. For the purposes of analysis, ocular hypertension was defined as an IOP greater than or equal to 21 mmHg in at least one eye.

Optic disc assessment. The optic disc of every eye was examined with the direct ophthalmoscope and, whenever possible, through a non-dilated pupil. The cup-disc ratio (CDR) was judged by contour (and not by colour). Three categories of CDR were recorded ($CDR \leq 0.3$, $CDR > 0.3$ and ≤ 0.5 , and $CDR > 0.5$) for both the horizontal and vertical meridian.

Refractive status. Determination of refractive status was made according to the subject's distance spectacles and recorded as emmetrope ($+2.00$ to -2.00 dioptres), hypermetrope ($+2.25$ dioptres or more), myope (-2.25 to -5.00 dioptres), and high myopes (more than -5.00 dioptres). The glasses were tested with a lensometer by an ophthalmic nurse or optometrist.

The χ^2 test, analysis of variance, and t test methods were used to assess statistical significance.

RESPONSE RATE

Of the 4993 who received invitations 2594 (53%) responded. A survey of a sample of the non-respondents was conducted, the results of which are reported elsewhere.³ In short, a comparison of socio-demographic characteristics of respondents with non-respondents indicated that there was no significant difference in the composition of the two groups in terms of sex or country of birth. However, the respondents were younger than the non-respondents (χ^2 test, $p < 0.001$). The respondents had a smaller proportion of persons over 70 years of age than non-respondents (12.1% versus 19.2% respectively). In a similar manner the respondents had a larger proportion of persons between the ages of 40 and 49 (38.1% versus 36.7%) and between the ages of 50 and 59 (30.5% versus 25.3%) than non-respondents.

Results

The intraocular pressure was measured in 2547 people (5068 eyes). One hundred and fifty five of the persons with IOP measurements available were found to be ocular hypertensives (21 mmHg or more in at least one eye). The prevalence of ocular hypertension in the screened population was therefore 6.1%.

The mean and standard deviation of the IOP of the right eye was 14.96, SD 4.24, mmHg, of the left 14.86, SD 4.03, mmHg. The median for both eyes was 14 mmHg.

The mean IOP by age is presented in Table 1. The mean IOP was found to increase incrementally by age from 14.35 mmHg among subjects under 50 years old to 15.49 mmHg among those over 70 years. This difference in means was statistically significant ($p < 0.001$) as determined by a one-way analysis of variance.

There was no difference in mean IOP between males and females. The mean and standard deviation of the IOP of the right eye for males was 15.00, SD 4.51, mmHg and for females 14.94, SD 3.99, mmHg. The mean IOP was found to be significantly higher (t test, $p \leq 0.001$) among persons of North African or Asian birth than persons of European or American birth, 15.39, SD 4.42, and 14.53, SD 3.64, respectively. These results are presented in Table 2.

The age adjusted distribution of subjects by sex and country of birth was found to be significantly different ($p < 0.01$) among persons with raised IOP than normotensives. 9.8% of the 556 men and 7.5% of the 649 women born in Asia or Africa were found to have an IOP > 20 , whereas only 4.6% of the 691 women and 6.1% of the 659 men born in Europe or America had a raised IOP. These results are presented in Fig. 1 and Table 3.

The age distribution of persons with raised IOP was also significantly different (χ^2 test, $p < 0.001$) from that of normotensives. While over 9% of persons aged 70 years and above ($n=365$) had a raised IOP, only 3.2% of persons under 50 years of age ($n=878$), 6.0% of persons 50–59 years ($n=780$) and 8.4% of persons between the ages of 60 and 69 ($n=571$) had such elevation. These results are presented in Fig. 2 and Table 4.

INTRAOCULAR PRESSURE AND CUP-DISC RATIO

The four recorded CDR measurements, right hori-

Table 1 Mean IOP by age (right eye)

Age (years)	n	%	Mean IOP	SD
40–49	862	34	14.35	3.07
50–59	760	30	15.13	4.72
60–69	554	22	15.35	3.94
70+	357	14	15.49	5.67
Total	2533	100	14.96	4.24

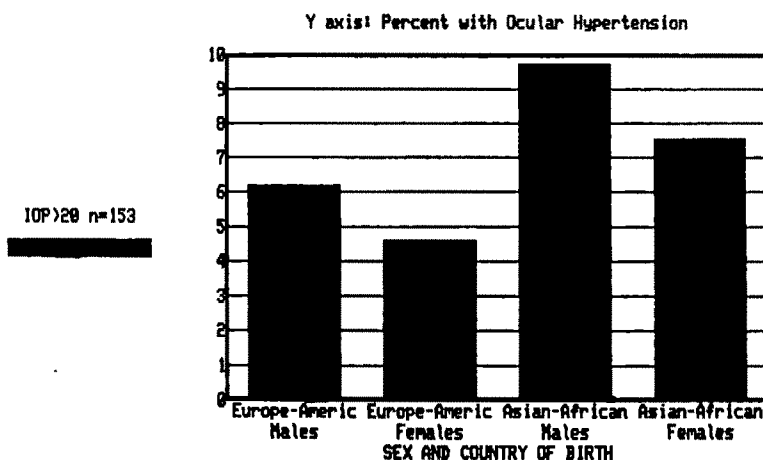
($F=9.84$, significance of $F < 0.001$).

Table 2 Mean IOP by country of birth (right eye)

Country of birth	n	%	Mean IOP	SD
American or European	1338	54	14.53	3.64
Asian or African	1166	46	15.39	4.42
Total	2504	100	14.93	4.04

$t=5.33$, $p < 0.001$.

Fig. 1 Age adjusted distribution of ocular hypertension by sex and country of birth. x axis: sex and country of birth. y axis: percentage with ocular hypertension. Solid: percentage with ocular hypertension.



zontal, right vertical, left horizontal, and left vertical, were collapsed into two new variables, CDR of the right eye, and CDR of the left eye as follows: >0.50 in at least one meridian, between 0.3 and 0.5 but no higher in at least one meridian, and <0.3 in both meridians.

We found a strong association ($p < 0.001$) between intraocular pressure and CDR. 23% of subjects with an IOP >21 mmHg had a CDR greater than 0.5 , whereas only 4.5% of those with an IOP less than 14 mmHg had a CDR >0.5 . These results are presented in Fig. 3 and Table 5.

The same association was found when the mean IOP was calculated for the three groups of CDR: a significantly higher (analysis of variance, $p < 0.001$) mean IOP was found among persons with a large (>0.5) cup-disc ratio. These results are presented in Table 6.

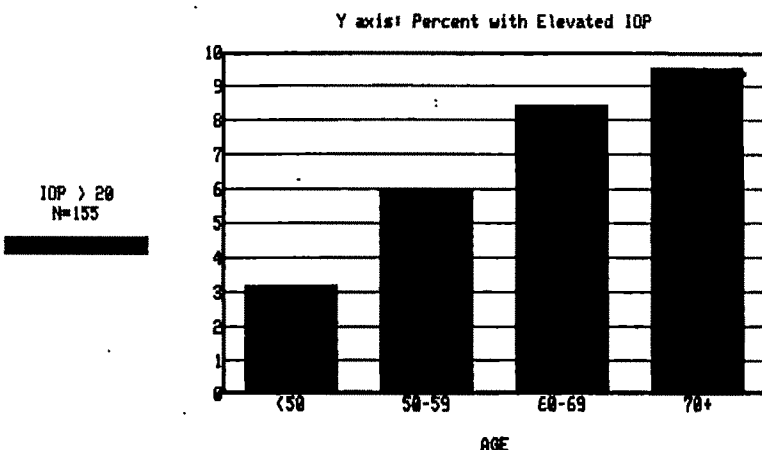
Table 3 Age adjusted distribution of ocular hypertension by sex and country of birth

Sex	Country of birth	Percentage ocular hypertension	n
Male	American and European	6.1	659
Male	Asian and African	9.6	556
Female	American and European	4.6	491
Female	Asian and African	7.5	649

Table 4 Age distribution of ocular hypertensives

Age (yr)	Percentage ocular hypertension	n
Less than 50	3.2	878
50 to 59	6.0	780
60 to 69	8.4	571
70 to 79	9.5	365

Fig. 2 Raised intraocular pressure by age. x axis: age. y axis: percentage with ocular hypertension. Solid: percentage with ocular hypertension.



(ANOVA: $F=9.84$, Significance of $F < .001$)

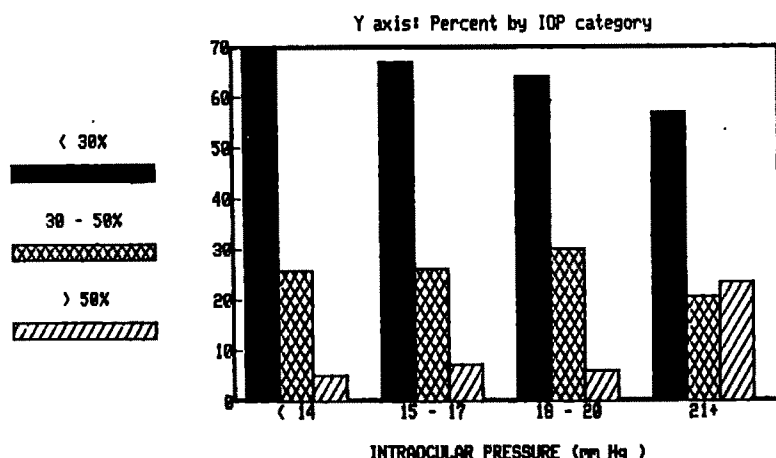


Fig. 3 Distribution of IOP by cup-disc ratio. x axis: intraocular pressure (mmHg). y axis: percentage by IOP category. Solid: cup-disc ratio <0.3. Cross hatching: cup-disc ratio 0.3 to 0.5. Single line hatching: cup-disc ratio >0.5.

INTRAOCULAR PRESSURE AND REFRACTIVE STATUS

The mean IOP was found to increase incrementally from a mean of 14.22 mmHg in hypermetropes to 15.44 mmHg in high myopes. This tendency was found to be statistically significant by analysis of variance ($p < 0.001$). This finding has been described in detail in a previous report.⁵

SYSTEMIC AND LIFE STYLE VARIABLES

Age adjusted odds ratios (OR) and confidence limits (CI) were calculated for the association of raised intraocular pressure with the cardiovascular risk variables and other conditions by the Mantel-Haenszel pooled odds ratio across age strata and are presented in Table 7. The odds ratio of a person having a raised IOP with a history of glaucoma in the family is over twice that of a person without a history of glaucoma in the family (OR=2.32, 95% CI 1.35 to 4.00). The odds of a diabetic or a person with a sedentary life style having ocular hypertension were one and a half times that of a non-diabetic or active person OR=1.58 and 1.41 respectively. Persons with cardiovascular disease or haemodynamic shock had lower odds of having ocular hypertension than persons without the condition, OR=0.51 and 0.69 respectively. Systemic hypertension was not found to be associated with a raised intraocular pressure. It should be noted that all the confidence intervals, except for that of history of glaucoma in the family, included 1.

Analysis of variance was used to examine the relationship between mean IOP and other ocular, demographic, and medical conditions. Each variable that was associated with the dichotomous IOP variable (IOP > 20 mmHg or IOP < 21 mmHg) was entered into an analysis of variance test. Age, physical activity, diabetes, CDR, and refractive

Table 5 Distribution of IOP by cup-disc ratio

IOP (mmHg)	Right cup-disc ratio							
	<30%		30-50%		>50%		Total	
	n	%	n	%	n	%	n	%
<14	845	68.6	331	26.9	56	4.5	1232	100
15-17	463	66.8	185	26.7	45	6.5	693	100
18-20	267	66.9	109	27.3	23	5.8	399	100
21+	69	57.5	23	19.2	28	23.3	120	100
Total	1644	67.3	648	26.5	152	6.2	2444	100

Table 6 Mean IOP by cup-disc ratio (right eye)

Cup-disc ratio	Mean IOP	SD	n
<0.3	14.83	4.02	1632
0.3 to 0.5	14.85	3.67	641
>0.5	17.28	6.70	146

Analysis of variance $F=24.00$, significance of $F < 0.001$.

Table 7 Age adjusted percentage prevalence of raised IOP by condition

Condition	Percentage of persons with IOP ≥ 21 mmHg		Odds ratio (95% confidence limits)
	Has condition	Does not have condition	
Hypertension (n=2542)	7.2	5.8	1.06 (0.98-1.15)
Diabetes (n=2543)	10.5	5.7	1.58 (0.81-3.06)
Cardiovascular disease (n=2538)	5.0	6.3	0.59 (0.27-1.25)
Haemodynamic shock (n=2530)	4.4	6.3	0.69 (0.36-1.32)
Lifelong sedentary life style (n=671)			
Sedentary versus marked physical activity	8.8	5.2	1.41 (0.57-3.47)
Glaucoma in family (n=2333)	11.4	5.6	2.32 (1.35-4.00)

Table 8 Analysis of variance: mean intraocular pressure of the right eye

Independent variables	F value	Significance of F
MAIN EFFECTS		
Cup-disc ratio	21.19	0.001
Physical activity	7.54	0.001
Refractive status	5.82	0.001
Diabetes	5.23	0.021
Age (covariate)	11.49	0.001

$R^2=0.044$.

status were each independently associated with a mean IOP after controlling for all dependent variables in both the right and left eye. These results are presented in Table 8. Family history of glaucoma was substituted for diabetes in an analysis of variance and found to be significant ($p=0.013$) in the left eye, but not significant ($p=0.061$) in the right eye. Systemic hypertension was not found to be independently associated with mean IOP in either eye ($p>0.05$) when substituted for diabetes in the analysis. Two-way interactions were examined between each independent variable in each analysis. The only interactions that were found to be consistent in terms of statistical significance in both eyes were those between physical activity and refraction ($p<0.001$) and refraction and diabetes ($p>0.05$). The amount of variance explained by the models was between 3 and 6%.

Discussion

There have been several population based studies from which to estimate the prevalence of raised intraocular pressure. The prevalence estimates of this study, 6.1% for IOP $\geq$ 21 mmHg, compare well with other studies despite somewhat different methods of measurement in each study.

These estimates are based on 2594 persons or only 53% of the target study population. However, little difference was found between the age and sex distribution of respondents and non-respondents. It might be expected, however, that persons with eye problems or relatives with eye problems would be more likely to participate in the screening. The estimate of prevalence of raised intraocular pressure in the screened population might therefore be an overestimate of the prevalence in the general population. On the other hand, since persons over 70 years old are relatively underrepresented in the screened population, our estimate of the prevalence of elevated intraocular pressure is likely to be an underestimate of the prevalence in the general population.

The increase in mean IOP with increasing age, cup

disc ratio, and myopia shown in our results also confirms evidence from other studies.^{6,7}

Although the differences in IOP by age were statistically significant, the actual differences were small and therefore the clinical importance questionable.

It is not clear why persons born in Asia or Africa were found to have higher intraocular pressure than those born in Europe or America. The difference may be related to a darker iris pigmentation among persons from Asia or Africa. Several investigators have found that segments of the population, particularly blacks, tend to have a higher intraocular pressure than whites.^{3,8,10} Hiller *et al.*⁹ also found that iris pigmentation was associated with mean IOP, even after controlling for race. On the other hand Shiose and Kawase¹¹ have found that the distribution of IOP among the Japanese is generally lower than that of western societies. Since iris pigmentation was not assessed in this study, it is impossible to determine whether this or other factors are associated with the difference in mean intraocular pressure.

Positive associations between increased IOP and diabetes, glaucoma in the family, and systemic hypertension have been reported by others,^{4,10,12} some even showing an association between IOP and blood pressure.^{4,10,11}

We found diabetes to be associated with the mean IOP but not with ocular hypertension, a possible reason for this being the somewhat arbitrary cut-off point of 21 mmHg which defined ocular hypertension in this study.

Our study did not confirm the association between IOP and systemic hypertension previously reported.^{4,10} There might be two reasons for this.

(1) We defined systemic hypertension based on the self-reported taking of antihypertensive medications and not based on a blood pressure measurement as other investigators; and (2) there was a relatively small number of persons with systemic hypertension and/or raised IOP. Therefore conclusions about the association between IOP and systemic hypertension based on this study would be tentative at best.

Refractive status has been shown to be associated with intraocular pressure^{7,13-15} and was therefore included in the analysis of variance.

There has been some discussion of the accuracy and reproducibility of test results obtained during screening for glaucoma.^{2,16-19} Interobserver variations in tonometry and optic disc assessment were evaluated on 103 respondents during this screening process and the results are published elsewhere.²⁰

In conclusion, this study lends further support to the hypothesis that intraocular pressure is associated with age, country of birth (ethnic origin?), cup-disc ratio, refractive status, glaucoma in the family, and

diabetes. However, there are probably many other as yet unidentified factors that contribute to the variation of mean IOP in a population as indicated by the small amount of variance attributed by the analysis of variance to the factors investigated in this study.

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Intraocular pressure rise after argon laser trabeculoplasty

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SUMMARY Eighty-four eyes received 107 argon laser trabeculoplasty treatments at Beth Israel Medical Center between 1982 and 1984 for advanced primary and secondary glaucoma. The prelaser mean pressure was 20.25 mmHg. Pressures taken 1½ hours postoperatively varied widely: the pressure rose after 47 treatments and fell or remained the same after 60. Significant increases in pressure occurred in 10 eyes, after 12 treatments; 42% of these had received burns of 0.8 watts or greater. Pressure changes were correlated with laser burn energy level. Both patients who had significant increases in pressure initially were retreated again—in the same eye—at another time had similar increases in postoperative pressure again, even with lower energy levels. Comparison with the results of previous reports highlights the advantages of limited treatment to the anterior trabeculum with low energy levels.

Laser trabeculoplasty (LTP) is of benefit to patients on maximum medical therapy whose condition is considered to be out of control. Laser therapy may allow the withdrawal of systemic or topical agents and sometimes postpone invasive surgical filtering procedures. The ability of LTP to lower intraocular pressure has gained it wide acceptance as a surgical alternative. While long term results are not clearly defined, the effects of LTP may be lessened by short term complications that include iritis, peripheral anterior synechiae, and visual field loss.¹

An immediate postoperative rise in intraocular pressure has been recognised as a serious complication of LTP, since candidates for the procedure belong, by definition, to a group particularly susceptible to pressure elevations. Some investigators have attributed loss of field and central vision to these transient pressure rises.² It has been suggested that these pressure elevations are related to the placement, extent, number, and configuration of burns on the trabecular meshwork as well as to their energy level. The limitation of treatment to half of the angle was originally conceived in an attempt to avoid such acute pressure changes.

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Material and methods

Between June 1982 and June 1984, 84 eyes of 59 patients were treated at the Beth Israel Medical Center for advanced primary and secondary glaucoma. Twenty-three eyes were retreated: 107 treatments were made in all. The mean age of the patients was 69.5 years, range 50 to 86. Seventy-five treatments were given to eyes with uncontrolled chronic open angle glaucoma (Table 1). Patients previously operated on and with secondary glaucomas were not excluded. All patients had marked damage of the optic nerve and advanced visual field loss. All were receiving the maximum tolerated medical therapy and were candidates for filtration surgery or other surgical intervention. The standard preoperative medical regimen included a miotic (pilocarpine or carbachol), epinephrine or propine, timolol, and a carbonic anhydrase inhibitor (either acetazolamide or methazolamide). In seven

Table 1 *Diagnosis of eyes treated*

Chronic open angle glaucoma	67
Pigmentary glaucoma	4
Low tension glaucoma	6
Pseudoexfoliation glaucoma	6
Glaucoma secondary to uveitis	1

cases laser surgery was performed because patients could not tolerate maximum medical therapy with side effects from miotics, carbonic anhydrase inhibitors, or beta blockers. Twenty-eight patients were male, 31 were female, and all were white. However, all the eyes treated by argon laser had pilocarpine 3% or carbachol 1.5% eye drops instilled immediately prior to laser treatment.

Surgery was performed on all patients by ML using a Coherent System 900 Argon laser photocoagulator. The patient was seated at the slit-lamp and a drop of topical tetracaine instilled. An antireflective-coated Goldmann three-mirror lens was placed on the eye with methylcellulose. The duration of exposure was 0.1 second, and burns were spaced evenly over the anterior half of 180° of the trabecular meshwork with a spot size of 50 µm. Power was titrated to a minimum on the basis of patient reaction. The criterion for the proper burn was blanching of meshwork. The mean laser power setting was 0.67 watt. Power output at the slit-lamp measured 90 to 95% of the meter readings as measured by external output meter calibrated for the Coherent Argon Laser and Zeiss slit-lamp and supplied by Coherent. The actual laser power administered was therefore minimally lower than the setting indicated. The number of spots varied from 50 to 55, and the mean calculated energy delivered was 3.6 joules (range of 3.0 to 6.25, standard deviation 1.7). Gonioplasty was performed as a preliminary procedure in seven patients: large 200 µm burns of 1.5 watts were applied to the peripheral iris, widening the inlet and helping to bring the meshwork into view.

The intraocular pressure (IOP) was determined for both eyes before the laser treatment. Postoperative monitoring was undertaken at one and one half hours and again later that day if a rise was found. All pressures were measured by Goldmann applanation tonometer with the patient seated at the slit-lamp. Excessive intraocular pressure was reduced with orally administered 50% glycerol, 2 ml per kilogram body weight. All preoperative glaucoma medications were continued in the postoperative period. Steroids were not used. Change in pressure was calculated by subtraction from preoperative pressure as measured on that day.

Following the suggestion made by Krupin *et al.*² a significant pressure rise was defined as either (1) an increase of 30% over prelaser pressure as taken that day, (2) a final pressure of greater than 30 mmHg, or (3) an increase of greater than 10 mmHg over preoperative pressure levels. Krupin *et al.*² used 'peak prelaser diurnal curve' IOP taken on another day as the baseline IOP measurement. We consider this to be not as relevant as the immediately preoperative pressure, which constituted our baseline

IOP pressure. This may have increased the number of cases considered significant in our series compared with theirs. Further, we considered our IOP rise to be significant if any one of our criteria were met, whereas Krupin *et al.* required that they all be met, namely, an increase of 30% over preoperative IOP, a rise to over 30 mmHg, and any increase of 10 mmHg over preoperative diurnal peak. Those cases of low tension glaucoma with a rise of 15 mmHg or more would not be included under such a definition unless they reached 30, despite the possible real risk to the patient. We considered that a low tension patient with a preoperative IOP of 10 or 15 mmHg was at risk if pressure rose to 29 mmHg despite the fact that the final pressure, for a chronic glaucoma patient, would not seem so great.

Results

The mean prelaser pressure was 20.25 mmHg (SD 6.2). One and a half hours after surgery the pressure was noted to rise in 47 (44%) cases. The pressure fell or remained the same in 60 cases. Pressure changes ranged from -7 mmHg to +30 mmHg. Twelve treatments (11.2%) resulted in significant pressure increases as defined by our criteria. Ten eyes and nine patients were involved. The average age of this group was 71.7 years (SD 7.8); five patients were male, four were female. Eight of nine had chronic open angle glaucoma, while one patient had glaucoma secondary to uveitis. The average laser power used in these 10 eyes was 0.81 watt (range 0.6 to 1.25, SD 0.21), compared with an average of 0.64 watt for all other patients (range 0.45 to 1.2, SD 0.24). Of the 12 total treatments in the study that used a laser power of 0.8 watt or greater, five (42%) resulted in significant rises in pressure. In contrast, of the 95 treatments using burns under 0.8 watt, only seven (7.3%) caused such a rise.

Of the four patients in the group of significant responders who had both eyes treated one had a bilateral pressure rise, while three had a high pressure rise in one eye only.

Three patients in the group of significant responders received two treatments to the same eye. Both of the patients who had an increased intraocular pressure on the first treatment suffered it again on retreatment. The other patient, who lacked such a response the first time, developed it only on second treatment to that eye.

Finally, among the 12 patients with high pressure response one eye had concurrent gonioplasty. An elevated pressure thus resulted in one of the seven patients with gonioplasty.

Twenty-three of the 84 eyes were retreated with a second LTP. Eighteen of these had chronic open

angle glaucoma, while one had pigmentary glaucoma and one pseudoexfoliation. Three had low tension glaucoma and one was aphakic. Two experienced pressure rises on both treatments, one only on the repeat treatment. No significant pressure rise was detected in any of the eyes with pigmentary (5), aphakic (4), low tension (9), or pseudoexfoliative (7) glaucoma.

Significant pressure rise was not linked to age, sex, or eye treated.

The long term results of laser treatment are found elsewhere. Response did not correlate with the occurrence of an early postoperative increase in pressure, as has been suggested by Weinreb *et al.*³ Of the 10 eyes and 12 treatments with a significant pressure rise six had successful results (from three to 12 months' follow-up), two eyes came to trabeculectomy, and two were lost to follow-up (Harrison R, Luntz M H, personal communication, paper in preparation). Of the nine failures in our total of 84 eyes two had significant intraocular pressure responses, and this occurred in 11% of successful cases.

Discussion

The risks of intraocular pressure rise immediately after laser trabeculoplasty have been highlighted earlier and are confirmed in this study. Previous suggestions for decreasing the danger of the response have included treating anteriorly, reducing the number and power of burns, and limiting treatment to one half or even one quarter of the meshwork.⁴ Treatments thus limited still result in increases of pressure. This study confirms the importance of technique and energy levels, with an incidence of significant pressure rises comparable to that of other studies done in a similar manner, and suggests that eyes sensitive to LTP will respond with intraocular pressure increases in a consistent manner on repeat treatment, which should therefore be undertaken with caution.

Wilensky and Weinreb⁵ demonstrated that a pressure rise occurs most often three to five hours postoperatively when the entire meshwork is treated, while it occurs earlier, at one and one half hours, if half of the entire angle is lasered. This was the time of pressure check in our series. In their series of 57 patients Krupin *et al.*² had two patients with significant pressure rises at four and seven hours that would have been missed when monitoring in the first hour only. It is clear that sensitive individuals at risk for central field loss would best be served by following pressure rise from 1.5 hours to seven hours after LTP.

Previous studies recording intraocular pressure

rise following LTP have varied according to definition and timing of recording pressure elevations, but still allow a suitable comparison with our own, especially with regard to techniques used. Weinreb *et al.*³ comparing different treatments, found that when using 360° anterior treatments of 0.8 watt, 10 out of 20 (50%) of eyes responded with a 'corrected' pressure change of +10 or greater. Using 180° treatment they found only one out of 20 (5%) to have such a change. It should be noted that this corrected definition tends to minimise change by subtracting rises occurring simultaneously in the other eye.

Hoskins *et al.* found 21 of 106 (19.8%) eyes to have an uncorrected pressure rise of greater than or equal to 10 mmHg. Their techniques varied within the study, divided between 180° and 360° burns as well as both anterior and posterior placement. They did note that the number of pressure rises was 9% if fewer than 65 burns were made and 29% if more were used.¹

Thomas *et al.* found that with 180° treatment 11.5% had pressure elevations greater than or equal to 10 mmHg above the baseline, compared with 37% with 360° treatment. These figures were accumulated over a three-week period however.⁶ Krupin *et al.*, including readings taken at four, seven, nine, and 20 hours as well, found that 14% had significant pressure elevations by their criteria.² Had their readings been made only at one hour the percentage would have been slightly lower.

Admittedly the time of comparison, power, and techniques have varied, but studies seem consistent in finding one range of risk when treating the entire angle and another lower range when treating half the angle. Despite differing definitions of the significant, our figure of 11.2% compares closely with other 180° treatments by Krupin *et al.* (14%), Weinreb *et al.* (11.5%), and Hoskins *et al.* (9%). Unlike the consistency in reports on the frequency of significant pressure increases, there is considerable variation among studies of the number of eyes showing intraocular pressure increases of more modest proportions. An increase of IOP of any magnitude was found in 25.3% by Thomas *et al.*, 34% by Hoskins *et al.*, 53% by Krupin *et al.*, and 35% by Weinreb *et al.* using 180° and 70% using 360°. Our finding of 47% falls near the average of these studies. It would appear that this number in itself is of little importance, and attention should be paid to large increases with potential damage to the eye.

Weinreb *et al.*³ considered that there was no reduction in the long term success of LTP with 180° treatments and also argued that results may suffer in the presence of acute postoperative pressure rises. It would appear that the final outcome in our study was not tied to the pressure elevation.

Less argon laser power was used in this study than described in other reports. Wise and Witter used 100 or 120 burns with 1.0 to 1.5 watts.⁷ While Krupin *et al.*² used anterior treatments and low powers similar to ours, with results comparable to our own, they did not demonstrate within the study of their own patients a correlation between power and pressure rise. In this series there was a significant correlation. Treatments using greater than or equal to 0.8 watt of power made up only 11.2% of the total number of treatments, yet were implicated in 42%, or 5 of the 12 treatments, with a significant pressure rise. The average laser power for responders was 0.78 watt compared with 0.64 for those not responding with a pressure rise. 42% of patients with treated energy ≥ 0.8 watt had a significant rise as opposed to 7.3% of those treated with < 0.8 watt.

Those who responded with a high pressure rise to one application did so again on repeat treatment, even when that second treatment was done at a lower energy level. The converse is not so: lack of a rise on initial treatment does not preclude its occurrence on retreatment. Similar statements cannot be made about the treatment of second eyes: only one out of four patients in the significant responders group who were treated bilaterally, had bilateral elevations.

In sum, patients should be followed up carefully after laser trabeculoplasty for immediate intraocular pressure increases. In an attempt to limit the extent of these increases we consider treatments are best maintained as close to 0.8 watt as possible. If higher levels are to be used, the prophylactic lowering of pressure preoperatively would seem to be advisable, especially in patients with field loss threatening fixation who are at high risk for further sudden optic nerve damage. It should be recalled, however, that Hoskins *et al.* found that pretreatment with acetazolamide did not diminish the intraocular

pressure rise, and other agents should be considered.¹

While flurbiprofen and prednisolone acetate 1% have not proved of great value in preventing pressure rise,^{8,9} attempts at varying concentrations of prostaglandin inhibitors to achieve an effect have been made. Richardson has suggested that frequent pilocarpine administration following LTP, 2% or 4% every two hours during the next 24 hours, may affect IOP rises.¹⁰ Since these patients are usually already on full medication, one wonders how the addition of these drops can be effective.

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Alterations of aqueous humour outflow following argon laser trabeculoplasty in monkeys

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SUMMARY We performed argon laser trabeculoplasty in one eye in each of three cynomolgus monkeys, leaving the contralateral eyes as controls. Four weeks later in both eyes of each monkey we infused cationised ferritin as a tracer of the aqueous outflow pathways for 30-40 minutes before fixation. In the control eyes cationised ferritin was found throughout the conventional aqueous outflow tract, labelling trabecular endothelial cells, both inner and outer walls of Schlemm's canal, and the collecting channels. No permeation of cationised ferritin through continuous cellular layers such as the corneal endothelium was detected. In the lasered spots of the treated eyes cationised ferritin was found to label the cellular sheet covering the trabecular scar at the lasered site, but no tracer was detected within the scar or in Schlemm's canal immediately beneath. In contrast in adjacent non-lasered regions the trabecular cells, the observed juxtacanalicular herniations, and the vacuoles of the inner wall as well as Schlemm's canal itself were extensively labelled. Our findings suggest impermeability to aqueous humour flow through the actual lasered lesion, with shift of flow to adjacent, non-lasered regions. In the normal monkey these regions compensate structurally and functionally in ways that may help to deal with this diverted flow.

Short term¹⁻³ and long term effects³⁻⁵ of argon laser trabeculoplasty have already been described by us and others. Four weeks following argon laser trabeculoplasty in monkeys we have observed that the lasered sites contain flattened scarred trabecular meshwork with a cellular extension over the scar and with a flat inner wall of Schlemm's canal beneath.⁶ Adjacent non-lasered regions were observed to have wide open intertrabecular spaces, with herniations of juxtacanalicular trabecular meshwork and the inner wall into and across the lumen of Schlemm's canal.

In order to study possible regional changes in aqueous outflow associated with these morphological changes we performed a tracer study using cationised ferritin *in vivo* four weeks after argon laser trabeculoplasty. This positively charged ferritin (MW 800 000) developed by Dannon *et al.*⁷ binds to negatively charged surfaces such as those that occur on a cellular membrane. This binding prevents the washout of the tracer during the fixation process and allows the delineation of the outflow routes. We have pre-

viously demonstrated that cationised ferritin can be used effectively as an ultrastructural tracer of aqueous flow patterns in the trabecular meshwork of the living monkey.⁸

Material and methods

Three sexually mature cynomolgus monkeys were used for this study. Argon laser trabeculoplasty was performed in the right eye of each with an energy setting of 400-700 MW, as described previously,¹ while the left eye remained untreated and served as a control. Intraocular pressures were determined with a Digilab pneumotonometer prior to and four weeks after laser treatment. Four weeks after argon laser trabeculoplasty the monkeys were anaesthetised with ketamine hydrochloride intramuscularly (10 mg/kg) followed by sodium pentobarbital intravenously (35 mg/kg). 2 ml (10.4 mg) of cationised ferritin in isotonic solution (measured pH=6.18, Sigma Inc., St Louis) was perfused into the anterior chamber as follows. The cationised ferritin was introduced through a 25 gauge needle into the anterior chamber from a reservoir at a height of 17 mmHg, while

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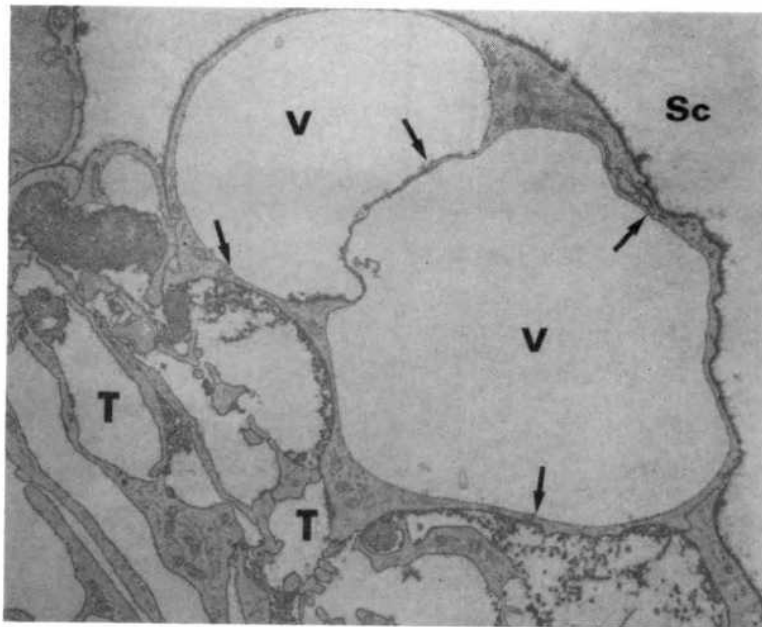


Fig. 1 Control eye. Cationised ferritin labels cellular membranes along the trabecular spaces (T) and inner wall of Schlemm's canal (Sc). Note uniform labelling of inner membranes (arrows) of giant vacuoles (V). TEM. $\times 6425$.

another reservoir containing Dulbecco's phosphate buffered saline with 5.5 mM added glucose was connected through a separate 25 gauge needle to the anterior chamber at a height of 13 mmHg. After 30–40 minutes of flow of ferritin through the anterior chamber from one reservoir to the other the egress route was clamped, and 3% glutaraldehyde in 0.1 M cacodylate buffer was infused into the anterior chamber for one hour at a pressure of 15 mmHg. The monkeys were then killed by an intravenous overdose of pentobarbital, and the fixative perfusion was continued for 20 minutes. The eyes were then enucleated, the anterior segments removed, and meridional sections of the iridocorneal angle were prepared. These tissue sections were postfixated in 1% osmium tetroxide with 1.5% potassium ferrocyanide, passed through graded alcohol concentrations, and embedded in Epon-Araldite. Thin sections were made (50 nm, silver-golden), stained with uranyl acetate and lead citrate, and observed with the JEOL JEM 7 electron microscope.

Results

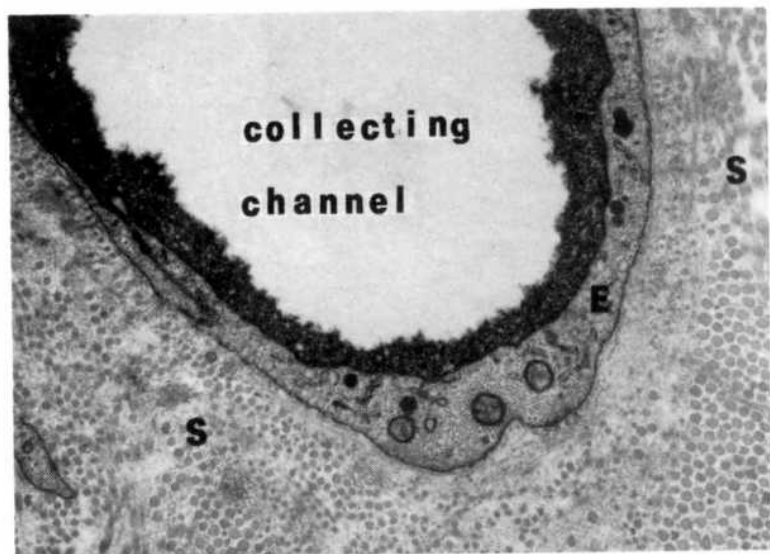
Four weeks after argon laser trabeculoplasty there was no change of intraocular pressure in the treated eyes (mean of 18 mmHg compared with mean of 17 mmHg in the control eyes).

In the control eyes cationised ferritin was found throughout the outflow tract. There was labelling along cell membranes of the trabecular endothelial



Fig. 2 Control eye. Corneal endothelium. Cationised ferritin labels the cellular membrane facing the anterior chamber (AC), but no tracer is detected in Descemet's membrane (D) or corneal stroma (C) beneath. TEM. $\times 4410$.

Fig. 3 Control eye. Collector channel. Note the thick layer of cationised ferritin labelling the luminal side of the endothelium (E), but no tracer is seen to permeate into the adjacent sclera (S). TEM. $\times 9695$.



cells, juxtacanalicular cells, the inner membranes of vacuoles, and the luminal side of the inner wall of Schlemm's canal (Fig. 1). Uniform labelling of the corneal endothelium was also evident, but no tracer was detected in Descemet's membrane or the corneal stroma (Fig. 2). A thick layer of cationised ferritin particles was found to label the endothelium of the

outer wall of Schlemm's canal and the collector channels, but no tracer was detected in the adjacent sclera (Fig. 3). In the eyes treated with argon laser trabeculoplasty lasered spots appeared as scarred trabecular meshwork, with extension of corneal endothelium over the flattened, collapsed beams and flat inner wall of Schlemm's canal. Cationised ferritin

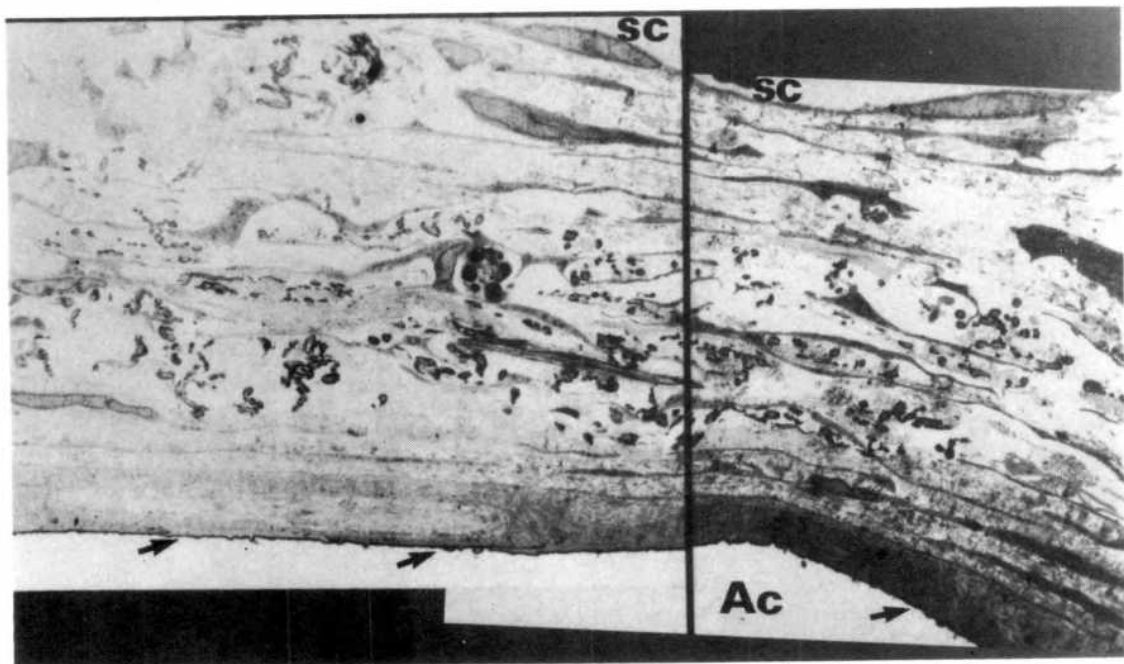


Fig. 4 Lasered spot, four weeks after argon laser trabeculoplasty. The trabecular meshwork is flattened and scarred. Cationised ferritin labels the cellular sheet extending from the corneal endothelium (arrows). No tracer is detected in the scar under this cellular cover nor on the inner wall of Schlemm's canal (Sc). AC=anterior chamber. TEM. $\times 1055$.

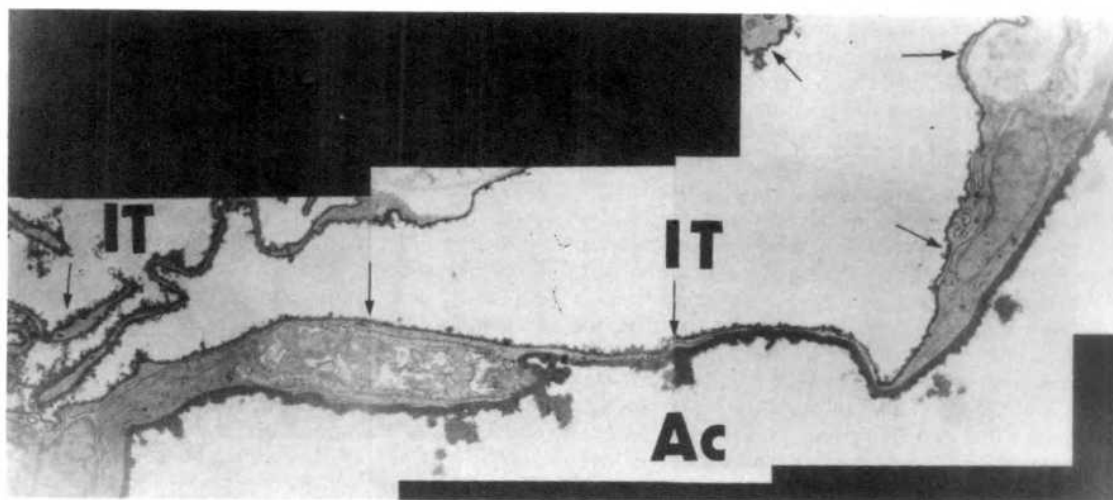


Fig. 5 Non-lasered region of eye treated with argon laser trabeculoplasty. Intertrabecular spaces (IT) are wide open and cationised ferritin labels trabecular endothelial cells on the beams (arrows). TEM composite. $\times 2015$.

labelled the cellular sheet, but no tracer could be detected within the scar or on the luminal surface of the inner wall of Schlemm's canal distal to the laser lesion (Fig. 4). In adjacent non-lasered regions the

intertrabecular spaces were wide open, with uniform labelling of trabecular endothelial cells lying over the beams (Fig. 5). Herniations of juxtacanalicular trabecular meshwork into Schlemm's canal were stained throughout their protrusions, with extensive labelling of the inner wall of Schlemm's canal (Fig. 6).

Discussion

In this study we searched for a correlation between the observed morphological changes and alterations of aqueous outflow within the angle of the anterior chamber following argon laser trabeculoplasty. For delineating the outflow routes, numerous tracers such as latex spheres,⁹⁻¹¹ thorium dioxide,^{9,12,13} and anionic ferritin particles^{14,15} have been used in the past. However, the main obstacle to the precise morphological description of the outflow pathways with those tracer particles is their tendency to wash out during perfusion with fixative. To overcome this problem we have used cationised ferritin for perfusion *in vivo*.⁸ Cationised ferritin is a positively charged molecule which binds to negatively charged surfaces such as cell membranes, a property which makes it capable of adhering strongly to the aqueous outflow routes, thus minimising washout effects. This tracer has already been used for labelling complex carbohydrates of the surface of the cornea *in vitro*^{16,18} and for labelling endothelial cells of iris vessels by perfusion or intravascular injection *in vivo*.¹⁵ We have previously described a uniform labelling with cationised ferritin of the conventional aqueous outflow tract of the monkey.⁸ Interestingly, however, no tracer could be detected in the trabecular spaces



Fig. 6 Non-lasered region of argon laser trabeculoplasty treated eye. Herniation of juxtacanalicular meshwork (arrows). Note the uniform thick labelling with cationised ferritin (arrowheads) of the inner wall of Schlemm's canal (Sc). P=probably a plasma cell. TEM. $\times 1765$.

beneath the operculum. Non-perfusion of the anterior trabecular meshwork underlying the operculum has already been proposed by others,¹⁸ and the absence of cellular labelling with cationised ferritin in this region suggests that this technique may be useful for identifying such regions of non-perfusion in the outflow tract.

In the present study we again found cationised ferritin to be a very reliable tracer which adheres to the aqueous outflow routes in a pattern similar to that of ruthenium red staining *in vitro*.¹⁹⁻²¹ Despite a pH of 6.18, cationised ferritin was found to be non-toxic to cells, probably owing to the buffering effect of aqueous humour *in vivo*. In the control eyes the tracer delineated the outflow pathways from the trabecular meshwork to the collecting channels. However, there was no penetration through the corneal endothelium into the stroma or through the endothelial lining of the outer wall of Schlemm's canal or the collecting channels into adjacent sclera, suggesting that cationised ferritin follows the route for the bulk outflow of aqueous humour.

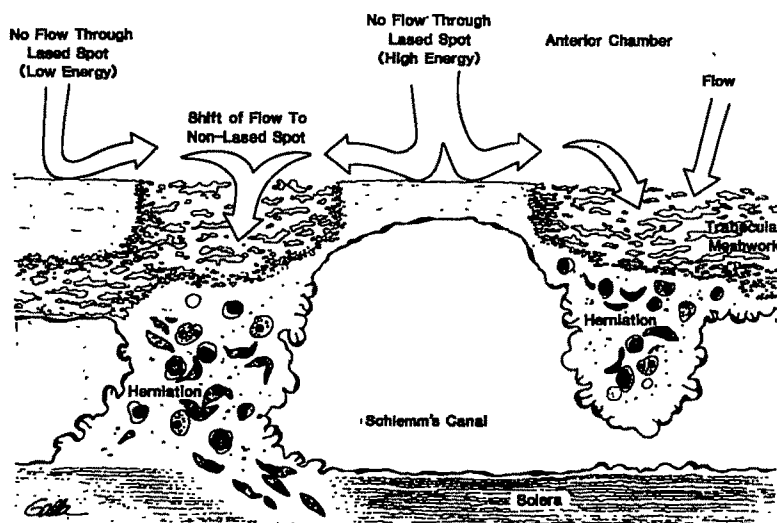
In the laser treated eyes scarred lasered spots were impermeable to cationised ferritin, which labelled only the cellular sheet covering the lesion. Within the time frame of the perfusion there was no staining of Schlemm's canal beneath the scar, indicating an absence of distal flow. However, the adjacent non-lasered areas were labelled throughout the outflow tract, including the lumen of Schlemm's canal, suggesting a shift of flow from the scarred lasered sites to the non-lasered regions. We propose, therefore, that in these non-glaucomatous monkeys, four weeks after argon laser trabeculoplasty the lasered scars of the trabecular meshwork are impermeable to

aqueous humour, which then must shift to the path of less resistance through the adjacent non-lasered trabecular regions. In a preceding report⁶ we demonstrated herniations of juxtacanalicular meshwork into and across the lumen of Schlemm's canal in the non-lasered regions of the trabecular meshwork. These herniations contained numerous vacuoles along the inner wall of Schlemm's canal and an abundance of chronic inflammatory cells in the trabecular spaces. The normal trabecular meshwork appears to compensate structurally and functionally to handle this diverted flow through the development of these extensive herniations and the formation of vacuoles, which probably provide an increased area for drainage into Schlemm's canal (Fig. 7). If the adjacent non-lasered trabecular meshwork is unable to adapt in this way, the intraocular pressure may be expected to rise, as has been shown to occur after more extensive confluent laser treatment of the trabecular meshwork in monkeys.^{22,23}

It is possible that stimulation of the trabecular cells such as increased turnover of extracellular matrix²⁴ or increased phagocytic activity,¹ which is triggered by argon laser treatment, may have a role in the efficacy of this procedure by removing 'clogging' debris from intertrabecular spaces. However, a decrease in trabecular cellularity, as shown in enucleated eyes after argon laser trabeculoplasty,²⁴ might contribute to a late decrease in the functional capacity of the trabecular meshwork and is of major concern. Such a loss of trabecular meshwork cells has been described in aging eyes²⁵ and also in glaucomatous eyes.^{26,27}

From our studies we still do not know whether glaucomatous eyes respond to argon laser trabeculoplasty as do the normal monkey eyes. In glaucoma

Fig. 7 Semischematic illustration of structural changes and aqueous flow alterations following argon laser trabeculoplasty in a normal monkey.



this treatment, when successful, results in intraocular pressure reduction even below prelasered level. If in the glaucomatous human eye the response of the trabecular tissue to argon laser is similar to what we have observed in the monkey, then it is also possible the herniations might be involved in some other biological process that we do not yet understand. Although mechanical shrinkage of collapsed beams may play a part in increasing outflow facility in glaucomatous eyes,²⁸ the biological effects and structural alterations that we observed may also be important.

In summary, we suggest that the morphological changes in the trabecular meshwork seen after argon laser trabeculoplasty are associated with regional changes in aqueous outflow. The end result in the normal monkey is to maintain the intraocular pressure unchanged despite the scarring of a substantial portion of the angle tissue. Whether these biological and morphological effects of argon laser trabeculoplasty play a part clinically in intraocular pressure reduction is still unclear, and studies of glaucomatous human eyes are needed.

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Parameters for neodymium-YAG laser trabeculotomy: an in-vitro study

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SUMMARY A Biophysic Médical Nanolas Q-Switched pulsed neodymium-YAG laser has been used to produce lesions in human trabecular meshwork in vitro. Sectors of corneoscleral tissue containing trabecular meshwork were suspended in a waterbath which had had a Trokel gonioscopic contact lens mounted into one side by means of a watertight seal. The laser was used to produce lesions in the trabecular meshwork on either side of each specimen. The energy levels delivered ranged from 0.5 to 7.0 mJ, and convergence angles of 10° and 18° were employed. The energy levels required to produce discrete lesions into the canal of Schlemm without perforating the underlying sclera were 3.0-5.0 mJ at the 10° convergence angle and 4.0-6.0 mJ at the 18° convergence angle setting. It is recommended that such data be determined for each type of laser prior to attempting short-pulsed laser internal trabeculotomy in patients with glaucoma.

The primary therapeutic endeavour in the management of chronic open angle glaucoma is the reduction of intraocular pressure. The greatest resistance to outflow of aqueous from the eye is provided by the trabecular meshwork.¹ Surgical procedures have thus been designed to bypass or diminish this resistance either internally by means of trabeculotomy² or externally by trabeculectomy.^{3,4}

It was initially expected that the argon laser would provide an effective means of producing a fistula between the anterior chamber and the canal of Schlemm,⁵ but these hopes were not realised because the scarring engendered by such treatment had the reverse effect and indeed provided the basis for experimental models of glaucoma.⁶ Argon laser trabeculoplasty, on the other hand, is thought to reduce intraocular pressure secondary to widening of the trabecular interstices between the focal scars caused by the laser applications.⁷

Recent clinical studies have indicated that short-pulsed laser trabeculotomy may effectively reduce intraocular pressure in patients with glaucoma,⁸⁻¹² though the potential efficacy of such treatment has Correspondence to Gordon N Dutton, Tennent Institute of Ophthalmology, Western Infirmary, Glasgow G11 6NT

been questioned.^{13,14} It is clear from the results of the early experimental work with the argon laser that, if a reduction in intraocular pressure is to be sustained, scarring and fibrosis of the trabecular meshwork must be avoided. To this end extensive experimental work with short-pulsed lasers has been carried out and reported in which the primary purpose has been to produce a 'clean' fistula between the anterior chamber and the canal of Schlemm.¹⁴⁻¹⁸

The efficacy and safety of the pulsed neodymium-YAG laser as a means of producing photodisruption in the eye has been established,^{19,20} and a wide range of such apparatus is marketed. Some laser manufacturers provide recommendations which indicate that their apparatus can effectively be used to produce an internal 'laser trabeculotomy'. However, such recommendations appear to be based on little if any experimental evidence. Indeed, the application of pulsed lasers for the treatment of open angle glaucoma is deemed to be solely investigational in the United States.²¹ The present study was conducted to establish whether such apparatus can effectively be used to produce a fistula into the canal of Schlemm in vitro and to establish the operating criteria required to achieve this end.

Materials and methods

The laser apparatus employed comprised a Biophysic Médical Nanolas Q-switched short-pulsed neodymium-YAG laser.

Human trabecular tissue was prepared from a donor eye from a 64-year-old male who had not suffered antecedent ocular disease. The eye was fixed in 3% cacodylate buffered glutaraldehyde, and 2 mm wide radial segments of corneoscleral tissue containing the trabecular meshwork were prepared. The ciliary body and iris tissue were removed by sharp dissection.

A small plastic waterbath was prepared and a Trokel gonioscopic lens (Ocular Instruments Inc.)

(compatible with pulsed neodymium-YAG laser use) was mounted with a watertight seal into one wall. The bath was filled with normal saline. Each specimen was mounted on cardboard and was sequentially immersed in the bath in such a manner that the trabecular meshwork could be clearly viewed through the centre of the Trokel lens by means of the laser slit-lamp microscope.

The laser was adjusted to each of the settings indicated in Table 1, and for each setting the laser was aimed and fired twice at the posterior trabecular meshwork at either side of each wedge shaped specimen. In each case the aiming beam was focused on the surface of the trabecular meshwork close to the cut edge of the specimen. This technique permitted subsequent evaluation of the lesions produced, in both the transverse and vertical dimensions.

Each specimen was reimmersed in 0.2 M cacodylate buffer and was subsequently prepared for scanning electron microscopy (Jeol JSMT200) by critical point drying and gold coating. The transverse dimensions of the lesions produced were measured from the electron micrographs by three observers and the mean and standard deviations of these triplicate recordings determined. The measurements taken comprised the transverse diameter of each lesion at the surface of the trabecular meshwork and the minimum internal transverse diameter. In some cases a symmetrical focus of compression of the trabecular beams was produced and only the surface measurement thus recorded. As considerable variation in the observers' estimates of the vertical dimensions of the trabecular meshwork was found, the vertical extent of the lesions produced was not measured but graded according to the legend to Fig. 1, in preference to using quantitative but imprecise measurements.

Table 1 Relates the convergence angles and energy levels delivered by the Q-switched neodymium-YAG laser to the characteristics and extent of the lesions produced in the trabecular meshwork

Convergence angle of 10°						
Specimen	Energy delivered (mJ)	Grade of lesion produced*	Surface diameter of lesion (µm) mean	Standard deviation	Deep diameter of lesion (µm) Mean	Standard deviation
1L†	0.5	1	349	27	—	—
R	0.5	2	94	2	54	13
2L	1.0	2	139	15	99	20
R	1.0	2	85	2	73	7
3L	2.0	2	121	4	59	4
R	2.0	2	73	7	54	13
4L	3.0	3	223	34	158	20
R	3.0	4	210	24	125	2
5L	4.0	4	311	27	230	0
R	4.0	4	315	21	243	0
6L	5.0	4	313	9	167	4
R	5.0	1	297	45	—	—
7L	6.0	5	177	8	92	0
R	6.0	5	272	4	113	12
Convergence angle of 18°						
8L	0.5	1	62	0	—	—
R	0.5	2	262	15	105	4
9L	1.0	0	—	—	—	—
R	1.0	0	—	—	—	—
10L	2.0	0	—	—	—	—
R	2.0	0	—	—	—	—
11L	3.0	1	195	4	71	21
R	3.0	1	149	24	79	4
12L	4.0	0	—	—	—	—
R	4.0	3	131	20	72	22
13L	5.0	2	221	25	121	22
R	5.0	4	264	31	239	8
14L	6.0	4	336	4	172	16
R	6.0	4	262	8	218	18
15L	7.0	4	256	13	247	15
R	7.0	5	324	37	130	41

*See Fig. 1 for classification †Side of specimen. The means and standard deviations of measurements were taken by three independent observers.

Results

The dimensions of the lesions produced in the trabecular meshwork in relation to the energy levels and convergence angles employed are shown in Table 1. The extent of the lesions produced in the trabecular meshwork was dependent upon the energy levels used. In most cases at low energy levels little or no effect was seen, the least observable disturbance being a focal area of apparent compression of the surface of the trabecular meshwork (Fig. 1A).

As the energy level was increased, a concomitant increase in the size and depth of the lesions produced was observed (Fig. 1B-F). At the 10° convergence angle setting lower energy levels were required to produce similar lesions to those obtained at the 18° convergence angle setting.

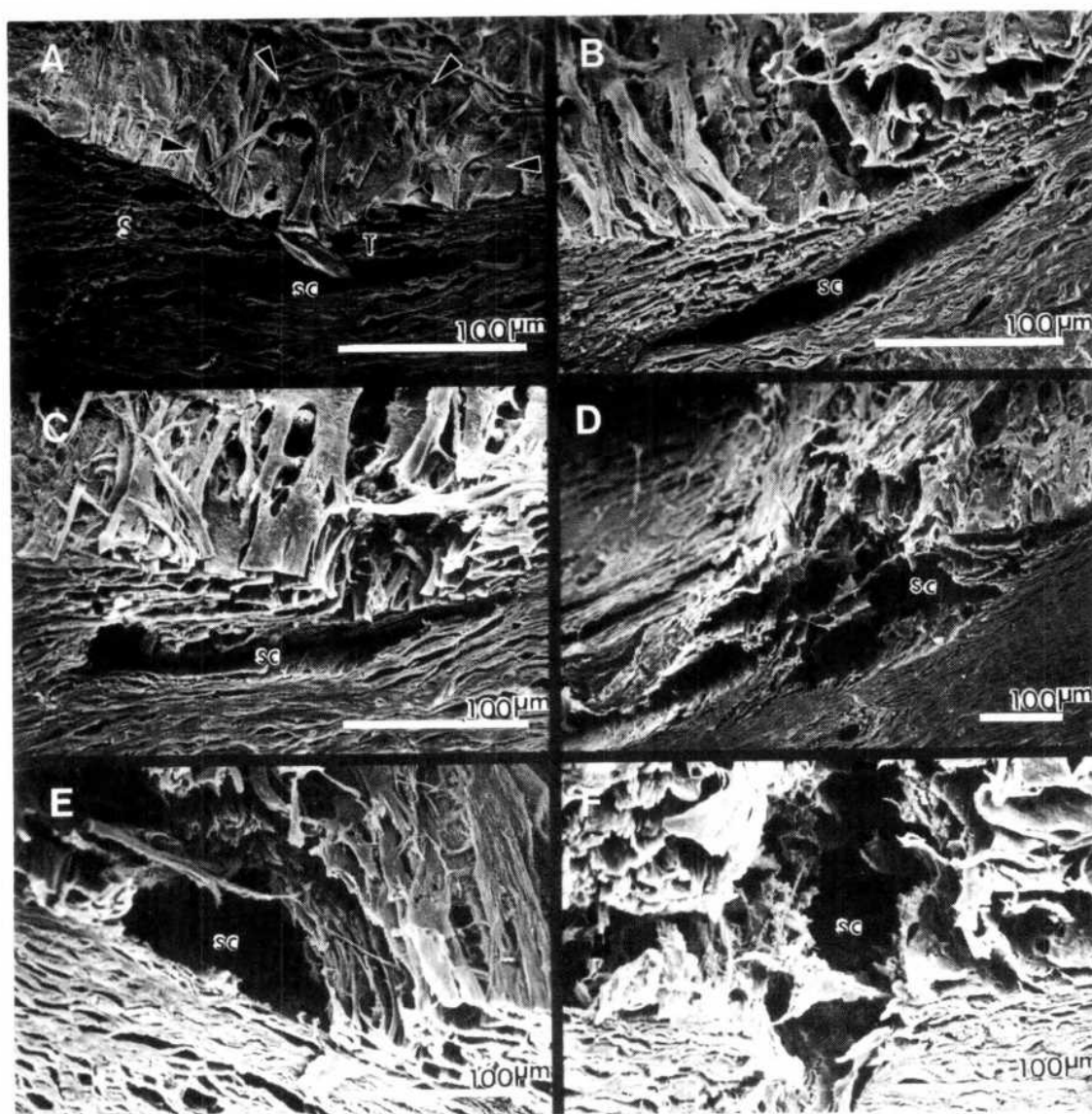


Fig. 1 Scanning electron micrographs of lesions produced in the trabecular meshwork by means of a pulsed neodymium-YAG laser (Grade 0=no lesion produced). A: Grade 1=Superficial trabecular compression (arrowheads) with minimal disruption. B: Grade 2=Superficial trabecular disruption with no penetration into the canal of Schlemm. C: Grade 3=Discrete focus of trabecular disruption with no penetration into the canal of Schlemm. D: Grade 4=Trabecular perforation through to the canal of Schlemm with slight disruption of the outer wall. E: Grade 5=Broad perforation through to the canal of Schlemm with limited disruption of the outer wall. F: Grade 5=Extensive disruption of the trabecular meshwork in which the perforation has extended through the outer wall of the canal of Schlemm into the underlying sclera. S=scleral spur. T=trabecular meshwork. sc=Canal of Schlemm.

Although at either convergence angle setting the trend was for wider lesions to be produced, at higher energy settings there was no linear relationship between the two parameters of lesion width and

energy delivered. However, with regard to the qualitative assessment as to the depth of the lesion produced there was a much clearer association between penetration and energy delivered.

The minimum energy settings which were found to produce a hole into the canal of Schlemm, with minimal damage to the outer wall of the canal were 3 mJ at the 10° convergence angle and 4 mJ at the 18° convergence angle. The gradation of tissue damage produced increased more gradually as the energy level was increased with the convergence angle of 10° than with the convergence angle of 18°.

Discussion

Clinical studies have indicated that a significant reduction in intraocular pressure can be produced in patients with chronic open angle glaucoma with raised intraocular pressure, by firing a short-pulsed laser at the trabecular meshwork.⁸⁻¹² Although initial reports have mostly been encouraging, the long term efficacy of such treatment has yet to be established. Moreover, each group of workers has studied different types of cases and has employed differing regimens of treatment. In theory, if a pulsed laser can be applied in such a way as to produce a fistula into the canal of Schlemm without either disrupting adjacent trabecular tissues or producing a hole through into the sclera, the likelihood of subsequent fibrosis and fistula closure may be diminished.^{17, 18} Recent work conducted with this end in mind has established that the exact operating criteria for the Q-switched neodymium-YAG laser must be precise.^{17, 18} The results of the present study indicate that analogous constraints apply to commercially available apparatus. If the energy level employed is too low, then no fistula into the canal is produced. Conversely, at high energy levels severe disruption of the trabecular meshwork and the canal of Schlemm is seen, with perforation into the underlying sclera. It is also evident that the convergence angle employed is a major determinant as to the nature and extent of the tissue damage produced. The Trokel lens has a convex surface and thus increases the convergence angle of the laser beam within the eye, and this must be borne in mind when interpreting the results described here.

The differences between the laser system employed for the present study and the system used in previous investigations in the same department^{17, 18} hinder precise comparisons of the results. In the previous studies energy levels of greater than 14 mJ were required to produce fistulae into the canal of Schlemm with a laser beam convergence angle of 6°.¹⁷ If similar mode structures of the laser beam are assumed for the present study, energy settings between 3 and 4 mJ at 10° and 18° convergence angles provide approximately the same energy density at the focal point.

The energy density at the laser beam focus varies

directly with the square of the cone angle of the convergent beam. It may thus initially appear paradoxical that higher energy levels are required for the higher (18°) convergence angle to produce the desired tissue effect. However, the narrower 10° convergence angle gives rise to a greater plasma length which is presumably required to produce a hole of sufficient depth.

Before treatment of this nature can be considered as a means of reducing intraocular pressure in patients with chronic open angle glaucoma many questions remain to be answered. How many fistulae into the canal of Schlemm and of what dimensions are required to reduce the intraocular pressure?²² What initial degree of raised intraocular pressure is required for a demonstrable reduction to be produced and sustained? Furthermore, morphological studies are required which assess the degree of replicability of the lesions produced in the trabecular meshwork for any given energy setting, as this has been shown in previous studies¹⁸ to vary considerably.

It is apparent that the optimal operating criteria required to produce a discrete and patent fistula into the canal of Schlemm are likely to vary and to be very precise. It is thus important that, unless appropriate experimental studies have been conducted, 'guidelines' as to what energy levels are required to produce an internal laser trabeculotomy should not be issued.

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Vitamin A deficiency in treated cystic fibrosis: case report

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SUMMARY We describe a patient with cystic fibrosis and hepatic involvement who, although on pancreatic extract, developed vitamin A deficiency, night blindness, and a characteristic fundus picture. All of these abnormalities were reversed by oral vitamin A supplementation.

Vitamin A deficiency has been reported in patients with untreated cystic fibrosis.¹ We report a patient on adequate pancreatin supplements without vitamin A who developed Vitamin A deficiency and night blindness. In this case cystic fibrosis was complicated by focal biliary fibrosis.

Case report

An 18-year-old black girl presented in October 1985 to the ophthalmic clinic complaining of difficulty in seeing in dim lights for some months. She had been diagnosed as having cystic fibrosis at the age of 8 months. In November 1983, when in hospital for investigation of dyspnoea and iron deficiency

anaemia, an abnormal liver ultrasound scan suggested infiltrative disease. Laparotomy was therefore performed, which showed diffuse irregular abnormality of the liver with scarring. Liver biopsy showed focal biliary and early multilobular cirrhosis (Figs. 1, 2) secondary to cystic fibrosis. Endoscopy at this time showed two low pressure oesophageal varices. After this admission to hospital the patient had intermittent problems with gastritis and postprandial abdominal distension. She was maintained on 14 Nutrizym (pancreatin and oxbile extract) tablets per day, acetylcysteine three times a day, Ketovite (multivitamin), Fortical (glucose drink), and the occasional addition of cimetidine.

Ophthalmic examination revealed on presentation visual acuities of R 6/12, L 6/5. There was no conjunctival or corneal xerosis; an inferonasal iris

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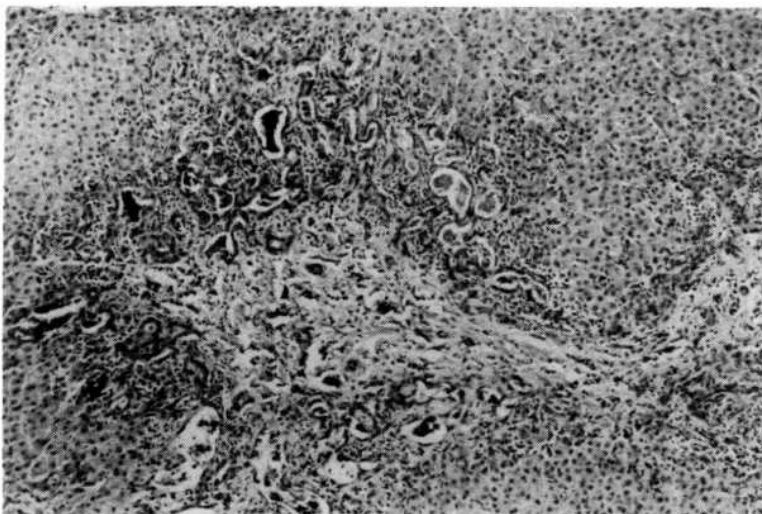
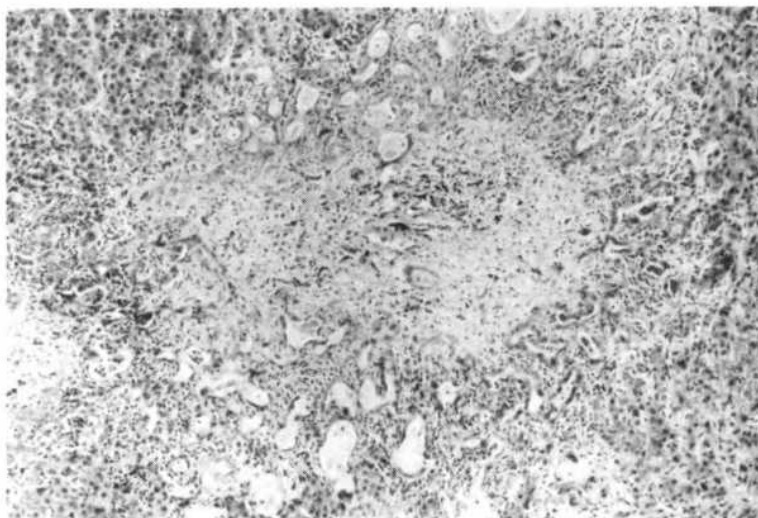


Fig. 1 Liver biopsy. Periportal fibrosis with ductular proliferation typical of hepatic involvement in cystic fibrosis. Haematoxylin and eosin.

Fig. 2 Liver biopsy. Note gross degree of periportal fibrosis. Masson trichrome.



coloboma was present in the right eye. Intraocular pressures were normal. Examination of the fundus showed very many discrete grey-white spots at the level of the retinal pigment epithelium (Fig. 3).

Goldmann perimetry showed mild peripheral constriction. An electroretinogram (ERG) showed depressed B wave amplitudes (Fig. 5). The electro-oculogram (EOG) showed a reduced Arden index of 136.5 ($n > 180$). Dark adaptation with a Goldmann Weeks Adaptometer showed an elevated final rod threshold (Fig. 6).

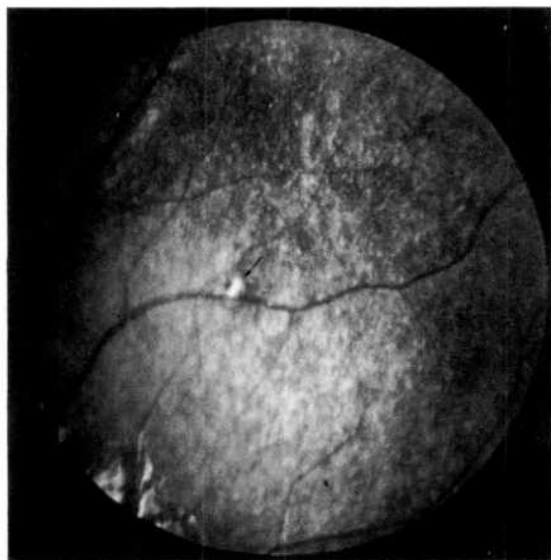


Fig. 3 Fundus photograph. Superotemporal area left eye. Grey-white spots at the level of the retinal pigment epithelium. Note area of retinal pigment epithelial atrophy which serves as a marker (arrow).

Laboratory studies included haemoglobin 9.8 g/dl, white cell count $3.8 \times 10^9/l$, haematocrit (packed cell volume) 0.30, mean corpuscular volume 79 fl, mean corpuscular haemoglobin 25.4 pg, mean corpuscular haemoglobin concentration 32.3 g/dl, urea 2.5 mmol/l, urate 2.2 $\mu\text{mol/l}$, total protein 8.5 g/dl, albumin 3.5 g/dl, globulin 5.0 g/dl, retinol binding protein 8 mg/l, and prealbumin 0.08 g/dl. The carotene level was depressed at 0.44 $\mu\text{mol/l}$ (normal 0.93–3.7 $\mu\text{mol/l}$), retinol was very low at <0.1 mg/l. Liver function tests were also abnormal, with bilirubin raised at 36 $\mu\text{mol/l}$, serum glutamic oxaloacetic transaminase 100 U/l, serum glutamic



Fig. 4 Fundus photograph. Four months after start of vitamin A therapy. Grey-white spots much less in evidence.

pyruvic transaminase 86 U/l, gamma glutamyl transpeptidase 56 U/l, and alkaline phosphatase also raised at 356 U/l.

The patient was started on vitamin A therapy. An initial intramuscular injection of vitamin A 300 000 IU was given accompanied by vitamin A tablets 5000 IU three times a day for one month, which was later reduced to one tablet per day.

Two months after starting treatment she stated that her night vision was improved. Fundus examination showed a decrease in the amount of grey-white spots (Fig. 4). Electrodiagnostic tests were repeated four months after first presentation and were markedly improved. The ERG showed normal B wave amplitudes (Fig. 5). The Arden index had improved to 261.36; repeated dark adaptation showed the final threshold returning to normal (Fig. 6). The serum retinol had improved to 0.17 mg/l.

Discussion

Vitamin A deficiency is nowadays rarely seen in cystic fibrosis owing to more effective therapy for increasing intestinal absorption. A consideration of the metabolism of vitamin A makes it clear how the deficiency may arise in cystic fibrosis patients. Normal dietary sources of vitamin A are β -carotene

from plants and vitamin A itself from animal tissue. β -Carotene is converted to vitamin A alcohol (retinol) in the body. Animal vitamin A may exist in either alcohol or ester forms. Transport from the intestine is via chylomicra to the liver, where vitamin A is stored as a retinyl ester. The liver is a major store of vitamin A, and it may be some months before a deficiency state becomes manifest. The vitamin is transported in the plasma from the liver to the tissues as an alcohol bound to a transport protein, retinol binding protein (RBP), which is itself complexed with prealbumin. Retinol binding protein is synthesised in the liver. Vitamin A metabolism may be interfered with at both intestinal and hepatic sites in patients with cystic fibrosis.

At necropsy in patients with cystic fibrosis hepatic involvement is seen in 15–20% of cases. The typical

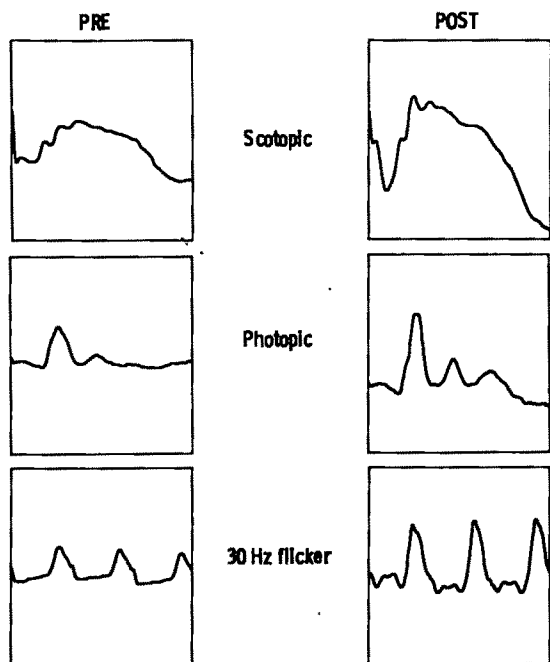


Fig. 5 Electoretinograms. Before and after vitamin A therapy. Improvement of B wave amplitudes following treatment.

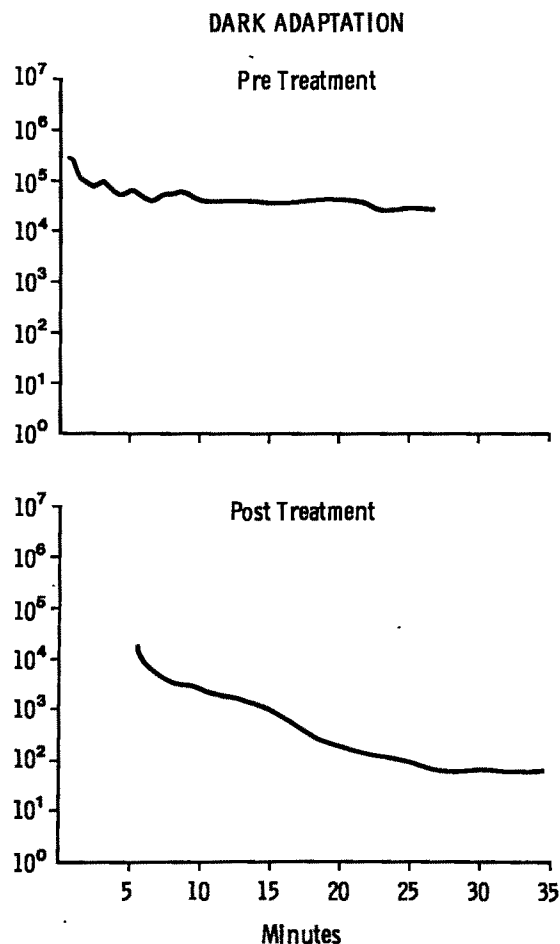


Fig. 6 Dark adaptation studies before and after vitamin A therapy. Decrease in final threshold with treatment is clearly seen.

lesion seen is a periportal fibrosis (also called focal biliary fibrosis). This may be accompanied by ductular proliferation. These lesions are well demonstrated in the liver biopsy from our patient. Progression of this process may lead to multinodular biliary cirrhosis. Patients with hepatic involvement in cystic fibrosis tend to develop vitamin A deficiency as the excess faecal bile acid is compounded by impaired bile acid synthesis.

That this patient did not have conjunctival xerosis is not unexpected, since such changes have been shown to be preceded by a fall in vitamin A levels and deterioration in dark adaptation.²

Vitamin A deficiency has been well documented in other types of liver cirrhosis,^{3,4} especially primary biliary cirrhosis. Walt *et al.*³ described three patients with late primary biliary cirrhosis and night blindness which responded to vitamin A therapy, while Russell *et al.*⁴ described abnormal dark adaptation in 26 patients with alcohol related cirrhosis which improved following vitamin A supplementation.

Petersen *et al.*⁵ described a patient with cystic fibrosis, night blindness, and xerophthalmia. In this instance the patient had failed to take pancreatic extract, and its reintroduction was sufficient to reverse the ocular abnormalities. Our patient in contrast was on full pancreatic supplementation and required added vitamin A.

The nature of the white spots seen in the retinal pigment epithelium of vitamin A deficient subjects is not known. Sorsby *et al.*⁶ produced similar lesions in rabbits fed a vitamin A deficient diet. Histologically

they appeared in the periphery, only later spreading centrally. They proved irreversible on intensive vitamin A therapy. The lesions in our patient and in a case described by Bors and Fells⁷ showed improvement of the fundus lesions with treatment.

All patients with hepatic involvement in cystic fibrosis should be on vitamin A supplement.

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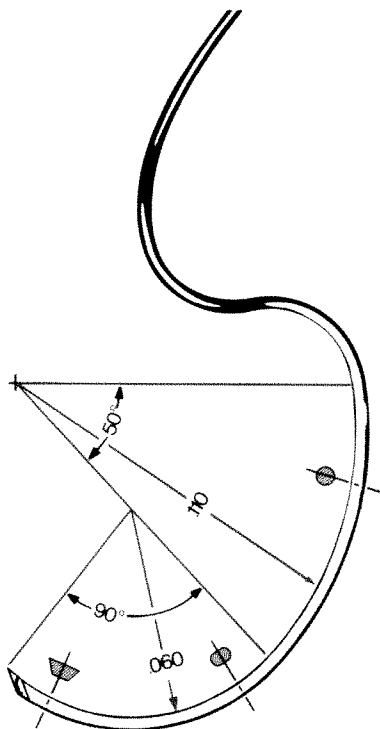
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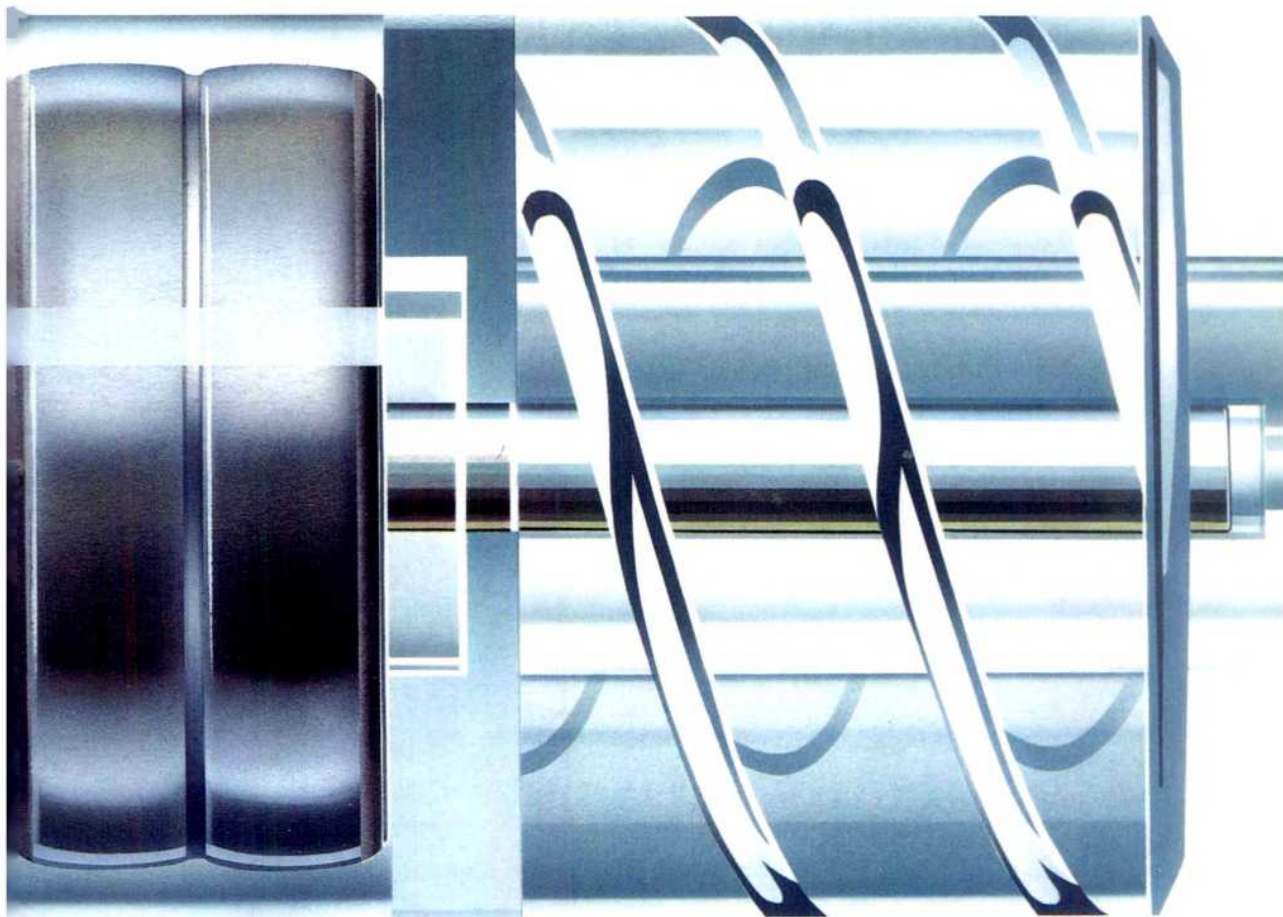
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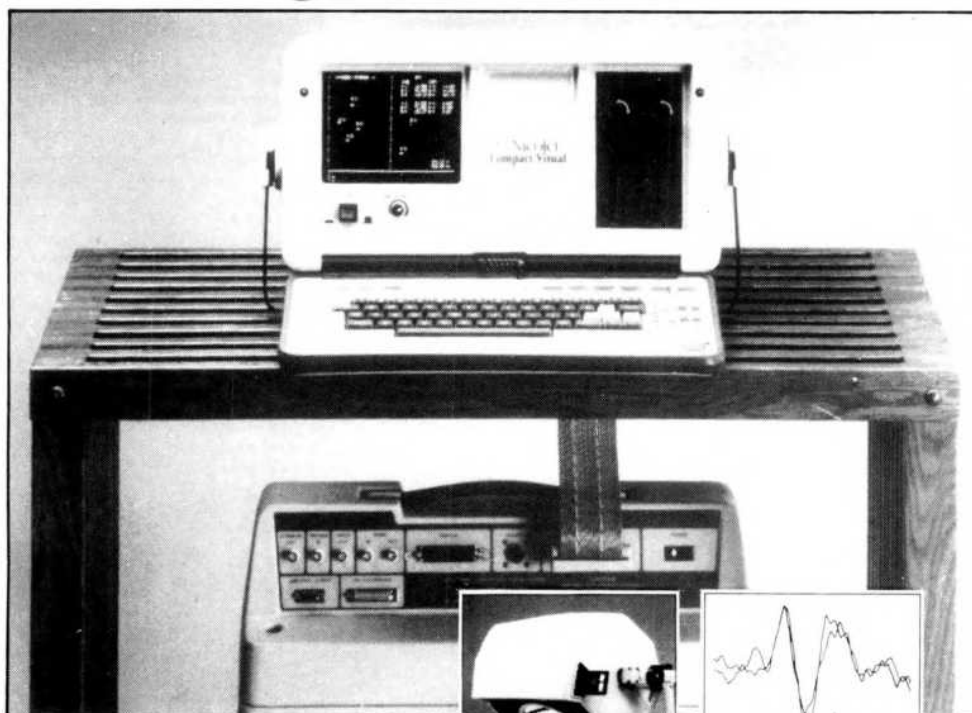
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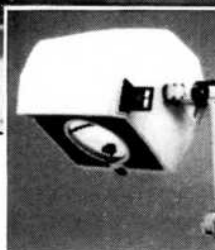
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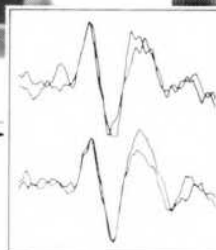
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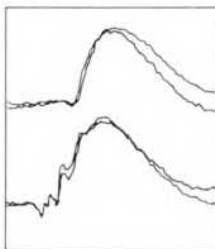
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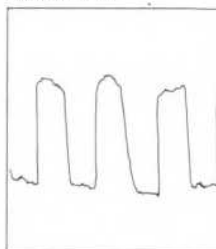
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Contrast sensitivity, acuity, and the perception of 'real-world' targets

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SUMMARY A major assumption underlying the use of contrast sensitivity testing is that it predicts whether a patient has difficulty seeing objects encountered in everyday life. However, there has been no large-scale attempt to examine whether this putative relationship actually exists. We have examined this assumption using a clinic based sample of adults aged 20-77 years. Contrast thresholds were measured for both: (1) gratings of 0.5-22.8 cycles/degree; and (2) real-world targets (faces, road signs, objects). Multiple regression techniques indicated that the best predictors of thresholds for real-world targets were age and middle to low spatial frequencies. Models incorporating these variables accounted for 25-40% of the variance. Although acuity significantly correlated with thresholds for real-world targets, the inclusion of acuity as a predictor variable did not improve the model. These data provide direct evidence that spatial contrast sensitivity can effectively predict how well patients see targets typical of everyday life.

Over the past two decades contrast sensitivity testing has grown in popularity as a clinical tool for describing visual disturbances associated with various ophthalmic disorders.^{1,2} Contrast sensitivity measurements can be particularly useful in diagnosis, since the shape and the height of the contrast sensitivity function (CSF) is vulnerable to pathological changes in the visual pathways. An assumption which often underlies the clinical use of the CSF is that it predicts whether a patient is likely to have difficulty in seeing visual targets typical of everyday life. Despite this widespread assumption, however, there has been no large-scale attempt to examine the validity of this putative relationship. The present study was designed to examine how contrast sensitivity measurements relate to the detection and identification of targets commonly encountered in daily experience.

There have been only a few earlier studies on contrast sensitivity and its predictive capacities. Typically these studies have centred on specific types of observers and have utilised relatively small samples. For example, Marron and Bailey³ report that, for low-vision patients, contrast sensitivity

could predict orientation and mobility on a test course. Ginsburg *et al.*⁴ found that Air Force pilots' CSFs predicted the distance at which air-to-ground targets were detected in an aircraft simulator. And finally Evans and Ginsburg,⁵ in a study on how aging relates to the visibility of road signs, found that contrast sensitivity was significantly correlated with the distance at which an observer could discriminate two highway signs.

These studies help to establish the validity of using contrast sensitivity as an indicator of the visibility of objects encountered in everyday life. Yet it would be helpful to know whether contrast sensitivity can be utilised in a clinical setting, where clinicians must make predictions as to what sorts of visual problems a patient might face in routine daily activities. In the present study we have used multiple regression techniques to examine this issue.

Subjects and methods

Patients (n=93) were recruited from the Primary Care Clinic and ranged in age from 20 to 77 years. As is evident from Table 1, each decade of age within this range was well represented in our sample. Binocular letter acuity, as measured by Sloan letters

Table 1 *Age distribution of sample*

Age	Sample size
20-29	16
30-39	20
40-49	15
50-59	14
60-69	15
70-77	14

at a distance of 3 m, ranged from 20/15 to 20/50. Our subject sample represented a range of diagnoses, from excellent ocular health to early cataract and macular degeneration. Since we were interested in obtaining a range of visual performance levels, we did not restrict our sample on the basis of acuity or diagnosis. This was considered to be desirable because this is a correlational study, and we did not want to narrowly restrict the range of measured threshold values.

Testing was divided into two parts: (1) spatial contrast sensitivity testing, and (2) the measurement of contrast thresholds for real-world targets. The order of presentation of these tests was counter-balanced across subjects. Each subject gave written informed consent before testing was begun.

CONTRAST SENSITIVITY TESTING

Contrast sensitivity was measured for a series of vertical, sinusoidal gratings of the following spatial frequencies: 0.5, 1, 3, 6, 11.4, 22.8 cycles/degree (c/deg). Gratings were stationary. These patterns were generated by a CS2000 contrast sensitivity system (Nicolet) and displayed on a television monitor. Mean luminance of the screen remained constant at 100 cd/m² during testing; surround luminance was 5 cd/m². Maximum contrast of the gratings was 0.50. The display subtended a visual angle of 4.2° × 5.5° at a viewing distance of 3 m.

Contrast thresholds for each spatial frequency were measured by a method of increasing contrast which was under computer control. Prior to the actual testing for a specific spatial frequency the patients were shown a suprathreshold preview of the grating they would subsequently be tested for. During the threshold measurement task, gratings were initially presented at a randomly determined, near-zero, subthreshold contrast, and then contrast was gradually increased. The patient was asked to push a button when the grating first became visible. After doing so, contrast returned to a randomly determined subthreshold level, and a new trial began. Eight thresholds were measured for each spatial frequency. Threshold performance was defined as the geometric mean of these eight thresh-

olds. Before any testing began we insured that patients understood the task by giving them practice at 0.5 c/deg and 6 c/deg. Since we were interested in the patients' performance under normal, everyday circumstances, they viewed targets binocularly with their habitual correction during contrast sensitivity testing and also during the task to be described below.

CONTRAST THRESHOLDS FOR REAL-WORLD TARGETS

Contrast thresholds were also measured for what we will refer to as 'real-world' targets. These targets were depicted on slides and were of three types: faces, road signs, and commonplace objects. Targets were relatively large, subtending from 4 to 6° of visual angle, and had an average luminance of 20 cd/m². Surrounding luminance was 5 cd/m².

The face targets were pictures of famous people, such as politicians and individuals in the entertainment media. The road signs were selected from the Alabama Motor Vehicle Study Book for drivers and consisted of frequently used signs such as the stop sign, pedestrian sign, and speed limit sign. The commonplace object targets consisted of objects fairly typical of our environment such as a lamp, a coffee cup, and a bicycle. Ten targets of each type were presented to patients.

Slides of these targets were projected through an optical system which allowed the subject to adjust the contrast of the target's image. This projection system, similar to one used in our earlier work,⁶ consisted of two slide projectors (Kodak Ektagraphic) positioned so that their beams travelled through a beam splitter, and then combined on a rear-projection screen (Plexicat). Fixed linear polarisers were positioned in front of each projector but were in orthogonal positions. One projector contained the target slide; the other projector had no slide, only an open aperture. Neutral density filters were used to equalise the luminance of the two projectors. Another polariser intersected the combined beams before they reached the screen. This polariser could be rotated via a step motor and allowed us to control the amount of light which came from each of the two slide projectors. In this fashion the contrast of the image could be varied from zero contrast to 0.90. Within this range the contrast varied linearly with the position of the polariser. The mean luminance of the target remained approximately constant regardless of changes in contrast.

The patient sat 2 m from the rear-projection screen. Viewing was binocular. Each target was initially presented at a randomly determined, near-zero, subthreshold contrast. The patient's first task was to increase the contrast of the target until

'something was just detectable on the screen'. The patient did so by pressing a button which was connected to the step motor's controller. The experimenter recorded the controller's digital read-out which indicated the position of the rotating polariser. (Each read-out value corresponded to a particular contrast level.) The subject was then asked to continue to increase the contrast of the target until he/she could identify the target. Thus for each slide we measured a detection threshold and an identification threshold. This threshold measurement procedure was carried out for each of 10 slides in each target type (faces, signs, objects). A patient's detection performances and identification for each target type were represented as the mean of the contrast thresholds for the 10 slides of that type.

Since we measured threshold for identification, we had to ensure that all targets were familiar to each patient before testing began. Prior to testing, the patients were asked to identify a large set of pictures of faces and road signs. We noted which ones were identified correctly, and then a subset of those were included in the threshold measurement procedure. We assumed that all patients would be familiar with the commonplace objects we selected for threshold testing, since they were items frequently encountered in daily life.

Results

Fig. 1 is a log plot of mean contrast sensitivity as a function of spatial frequency. In order to display the data in some meaningful fashion we have graphed a

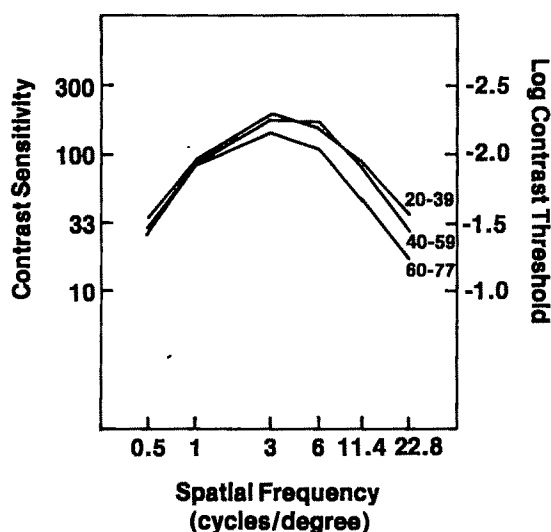


Fig. 1 Mean contrast sensitivity as a function of spatial frequency. Results are plotted separately for the three age groups: 20-39 years, 40-59, and 60 and over.

separate function for each of three age groups—20-39 years, 40-59 years, and 60 years and over. Contrast sensitivity is defined as the reciprocal of contrast threshold.

Sensitivity for the young and middle-aged patients was very similar, but the older age group had decreased sensitivity at intermediate and high spatial frequencies (at 6 c/deg, $F(5,87)=3.54$, $p=0.0058$; at 11.4 c/deg, $F(5,87)=5.91$, $p=0.0001$; at 22.8 c/deg, $F(5,87)=6.66$, $p<0.0001$). This general trend of a middle-to-high spatial frequency loss with increasing age during adulthood is in agreement with earlier work.⁷⁻¹⁰ However, it is important to note that in the present study we have confounded the age variable with disease. That is, there was no attempt to exclude subjects of any age who had ocular disease, because, since this was a correlational study, we were interested in recruiting a sample with a wide range of visual threshold levels. Thus, these data are not strictly comparable to those from our earlier work on contrast sensitivity,⁷ where we examined the effects of biological aging by carefully controlling variables such as disease and refractive error.

Fig. 2 displays how log contrast thresholds for detection and identification of real-world targets varied as a function of age. Panel A shows the results for the face targets, panel B for the sign targets, and panel C for the object targets. Fig. 2 illustrates that both detection and identification thresholds increase with increasing age in our sample (face detection, $F(5,88)=5.53$, $p=0.0002$; face identification, $F(5,88)=6.39$, $p<0.0001$; sign detection, $F(5,88)=8.70$, $p<0.0001$; sign identification, $F(5,88)=5.06$, $p=0.0004$; object detection, $F(5,88)=5.89$, $p=0.0001$; object identification, $F(5,88)=9.50$, $p<0.0001$).

MULTIPLE REGRESSION ANALYSES

The major question posed in this study is whether spatial contrast sensitivity measured in a clinic based sample can predict patients' contrast thresholds for real-world targets. To address this question we performed a stepwise multiple regression analysis (forward and backward stepping) on each dependent variable. This type of analysis reveals which independent variables best predict the obtained data. Table 2 lists the predictor (independent) variables that we evaluated. These variables included contrast threshold for each of the tested spatial frequencies (0.5, 1, 3, 6, 11.4, 22.8 c/deg). In addition two further variables were evaluated as predictors: acuity, since it is the traditional measure of pattern vision, and chronological age, since it is a readily available piece of information obtained when examining a patient. As discussed earlier, detection and identification contrast thresholds were measured for each of three types of targets—faces, road signs, and objects. We

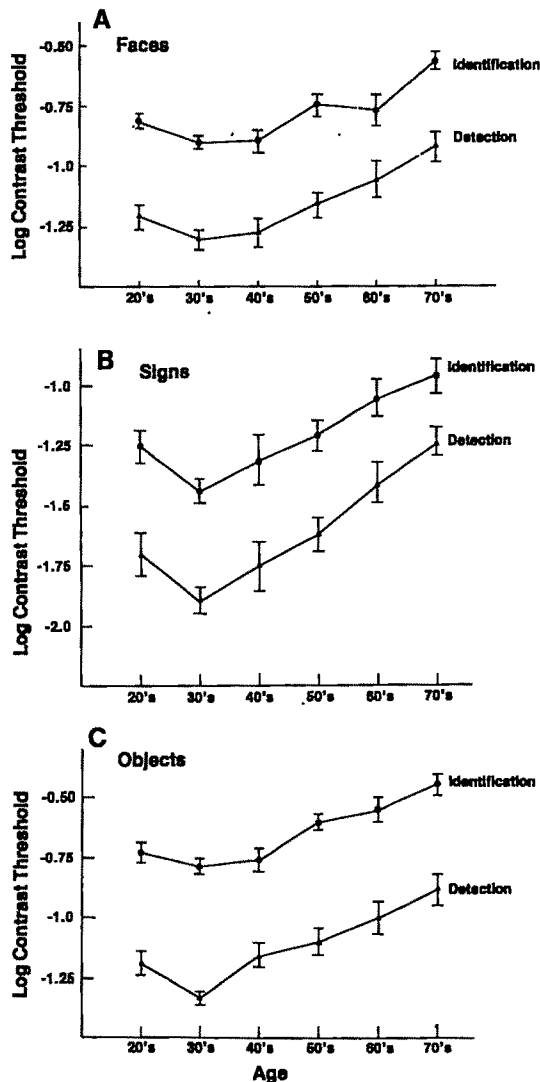


Fig. 2 Mean contrast thresholds for detection and identification of real-world targets, plotted as a function of age. Panel A shows the results for face targets; panel B for signs; panel C for objects. Vertical bars indicate two standard errors above and below the mean.

Table 2 Independent variables evaluated

Contrast threshold at:
0.5 c/deg
1.0 c/deg
3.0 c/deg
6.0 c/deg
11.4 c/deg
22.8 c/deg
Letter acuity
Age

therefore performed six separate multiple regression analyses to evaluate how effectively the independent variables listed in Table 2 predict each of the six dependent variables.

Table 3 lists the best-fitting model for each dependent variable. These are the models that emerged from a forward stepping technique in the regression analysis. (Backward stepping generated similar results.) The independent variables in each model are listed in order of their entry into the model. Also listed is R^2 , the percentage of variance in the data accounted for by each model. If an independent variable is not listed as a part of the model, the inclusion of that variable in the model did not significantly improve the model as indicated by the F ratio ($\alpha=0.05$ significance level).

There are a few important points to highlight. First, in the case of almost every dependent variable, 6 c/deg and age were the best predictors of contrast thresholds for the real-world targets. Adding further independent variables, such as higher or lower spatial frequencies did not significantly improve the model. The only exception to this general trend was the model for face detection, where age and lower spatial frequencies were the predictor variables. Secondly, a significant portion of the variance in each threshold task was accounted for by these models, ranging from 25% to 40% of the variance.

Thirdly, what is striking about these models is that they do not include acuity as a predictor, even though acuity is traditionally viewed as an important piece of information when assessing a patient's pattern vision. As displayed in Table 4, acuity did significantly correlate with all six of our contrast threshold measures for real-world targets. More specifically, poor acuity was associated with higher contrast thresholds. The question then is, why does acuity not appear as a predictor variable? It is important to note

Table 3 Best-fitting model for each dependent variable

Dependent variable	Independent variable	R^2 for model
Face detection	Age	0.29
	3 c/deg	
	0.5 c/deg	
Face identification	6 c/deg Age	0.25
Sign detection	6 c/deg Age	0.40
Sign identification	6 c/deg Age	0.30
Object detection	Age 6 c/deg	0.28
Object identification	Age 6 c/deg	0.40

Table 4 Correlation between acuity and various dependent variables

Dependent variables	<i>r</i>
Face detection	0.27
Face identification	0.31
Sign detection	0.38
Sign identification	0.28
Object detection	0.34
Object identification	0.41

Critical *r* (2-tailed, $\alpha=0.05$)=0.21.

that acuity is also highly correlated with age ($r=0.54$), which was an important predictor variable in the best-fitting models. It could be that once age has entered into the model, acuity adds very little additional information. Acuity may account for little variance beyond that already accounted for by the age factor. To evaluate this possibility we repeated the regression analyses on all six threshold measures for the real-world targets, but this time age was omitted as an independent variable. The best-fitting models emerging from these analyses are listed in Table 5. The general result was that acuity did emerge as a significant predictor in three out of the six threshold tasks, but it was never the first predictor (which was usually 6 c/deg). Furthermore, the models where acuity was forced into the model by excluding age as an independent variable accounted for less variance on average (24%) than the models which incorporated age as a predictor (32%).

Discussion

The results of this study indicate that spatial contrast sensitivity predicts whether patients are likely to have difficulty in seeing visual targets typical of everyday experience. In our study, if a patient had decreased sensitivity at middle-to-low spatial frequencies, that patient was also likely to have a decreased ability to see faces, road signs, and commonplace objects. It is important to note that the actual spatial frequency range which best predicts sensitivity for a real world target is likely to depend on the angular subtense (and thereby its spatial frequency content) of the real-world target in question. If our targets had smaller or larger visual angles (corresponding to greater or closer viewing distances in the real world), the spatial frequency range which best predicts their visibility would most likely be different than that reported here. The crucial point, however, is that spatial contrast sensitivity does systematically relate to the visibility of real-world targets such as those used in the present study. Clinicians can take advantage of this relationship by using contrast sensitivity testing to predict better the visual prob-

Table 5 Best-fitting model for each dependent variable with age omitted as independent variable

Dependent variable	Independent variable	<i>R</i> ² for model
Face detection	3 c/deg 0.5 c/deg	0.19
Face identification	6 c/deg	0.18
Sign detection	6 c/deg Acuity	0.32
Sign identification	6 c/deg	0.25
Object detection	6 c/deg Acuity	0.21
Object identification	6 c/deg Acuity	0.31

lems their patients are likely to encounter outside the clinic.

Since it was not the purpose of this study to identify the specific spatial frequencies involved in face perception, the spectral content of our stimuli were not measured. However, previous research has shown that lower spatial frequencies have a crucial role in face detection, while higher spatial frequencies are important in facilitating face identification.¹¹⁻¹³ Our data are consistent with this earlier work in that the best spatial-frequency predictors in face detection were 3 and 0.5 c/deg, whereas 6 c/deg was the best predictor in face identification.

In both the contrast sensitivity task and the threshold task for real-world targets, older adults tended on average to have higher thresholds than those of young adults. There has been some suggestion in the gerontological literature¹⁴ that older adults may be more cautious in their responses to perceptual stimuli. In a psychophysical experiment this contention could be characterised in terms of an older person possibly having a more conservative criterion for stating that a sensory signal is present. Thus in this view higher thresholds in older adults may be due to cautiousness in responding rather than to a real visibility problem. For the following reasons we believe that it is doubtful whether the age-related declines in sensitivity in the present work can be accounted for in this fashion. First, in regard to age-related changes in the spatial CSF, the higher spatial frequency loss in older adults reported here has also been reported in other studies using several different psychophysical methods,^{7-9,15} including a study using a criterion-free, forced-choice procedure.¹⁰ Secondly, as regards the threshold measurement procedure for real-world targets, an earlier study⁴ on age-related changes in face perception, using the same methodology as the present study, indicated that criterion effects had no role in older adults' elevated thresholds. This implies that the present

results, generated through the same procedure, are not due to criterion differences between young and older adults.

The contrast sensitivity levels in the grating task are for the most part higher than those for the real-world target task. This is probably due to a combination of factors, such as lower target luminance for the real-world targets, the periodicity and simplicity of the sinewave gratings, and the 'preview' grating before threshold measurement in the grating task (which presumably reduced the observer's uncertainty about the test target).

It is interesting that chronological age by itself was a powerful predictor of patients' thresholds for real-world targets. It is true that, in terms of the experimental design of the present study, age is confounded with disease, since patients were not excluded on the basis of diagnosis. Yet it is important to note that our study indicates that a patient's age can be at least as important in predicting some visual problems as are more complicated clinical measurements. However, further regression analyses indicated that, even within a single age group, contrast sensitivity can identify patients who have difficulty seeing real-world targets, implying that age by itself is certainly not sufficient information for the diagnosis of contrast sensitivity problems.

Although acuity was significantly correlated with contrast thresholds for real-world targets, the inclusion of acuity as a predictor variable did not significantly enhance the model. This finding is in agreement with the increasing number of studies which indicate that acuity often fails to predict the day-to-day visual problems patients face.^{6,16,17} Acuity measurements are particularly useful in carrying out refraction and in identifying difficulties in seeing detail, but much of our routine visual activity involves the detection and discrimination of larger objects in our environment. Spatial contrast sensitivity testing appears to be more useful to clinicians in identifying these latter problems.

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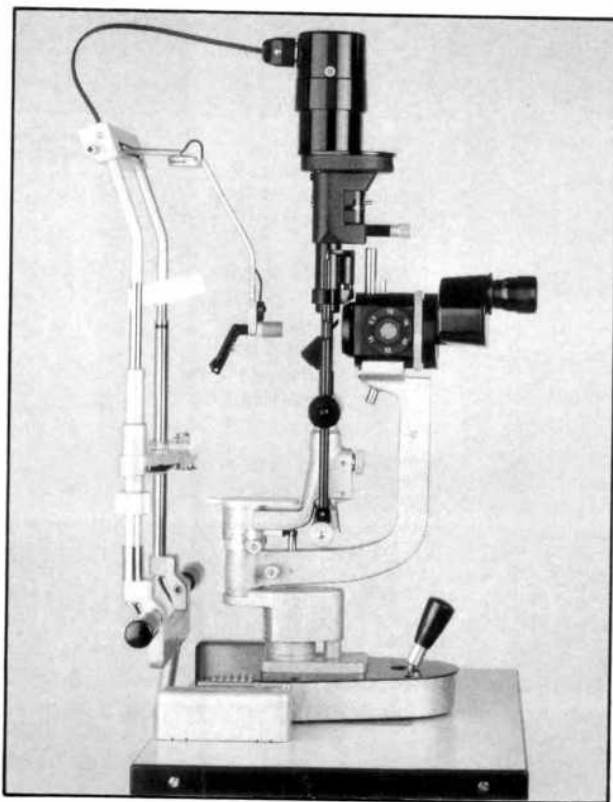
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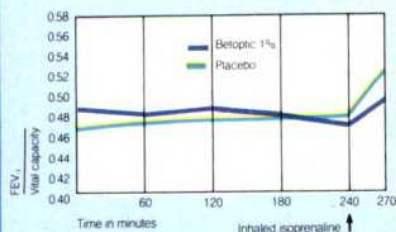
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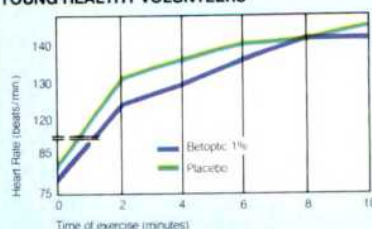


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AN EXERCISE INDUCED TACHYCARDIA STUDY IN YOUNG HEALTHY VOLUNTEERS

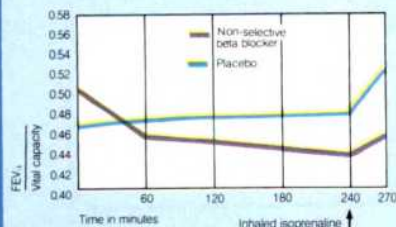


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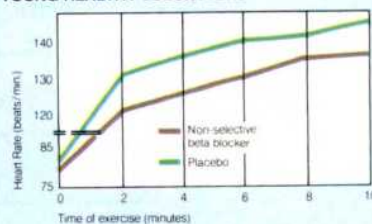
A PULMONARY STUDY IN ASTHMATIC PATIENTS



Graph adapted from Schoene, R.B., et al. Am. J. Ophthalmol 97 86-92, 1984.

Compare the effects which have been demonstrated on the heart and the lungs with some other ophthalmic beta-blockers 1 2 3 4

AN EXERCISE INDUCED TACHYCARDIA STUDY IN YOUNG HEALTHY VOLUNTEERS



Graph adapted from Atkins, J.M., et al. Am. J. Ophthalmol 99 173-175 1985.

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Assessment of the Catford drum in visual acuity testing and its use as a measurement of visual performance in low-vision patients

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SUMMARY Objective measurements of visual acuity were determined with the Catford drum in 82 eyes of patients in our Low-Vision Clinic who typically suffered from visual loss due to macular disease. The results were compared with subjective measurements of visual acuity by the Snellen chart. The findings indicated a significant overestimation of Snellen visual acuities by the Catford drum in 90.2% of eyes tested by a factor of 1.05 to 20.0, average 4.73. The correlation coefficient for the study was +0.40. This differs from the original results of Catford and Oliver in 1971. In addition, the Catford drum was used on follow-up visits in the same patients to assess 'visual performance'. The initial results showed an improvement in visual acuities when the Catford drum was used in 12 of 15 patients, while the Snellen acuities remained stable when retested after one month of basic instruction and use of standard low-vision aids. This improvement in 'Catford' acuity was by a factor of 0.3 to 10.0, average 4.08. This is thought to represent the patient's ability to learn the use of eccentric viewing or parafoveal retinal areas for vision. It confirms previous intuitive findings and helps to explain why low-vision patients seem to function at a higher level than expected from their Snellen visual acuities.

Many of our Low-Vision Clinic patients surprise us by the fact that their daily life performance is often so much better than might be expected on the basis of their Snellen visual acuity. Our current method of assessing visual acuity and presumably performance in low-vision patients is by means of a static subjective test, the Snellen chart.

We believe that in addition to the tested Snellen visual acuity fraction every patient has a certain level of 'visual performance' independent of this, which as we define it relates to the patient's ability to function and perform daily life tasks. Furthermore, visual performance is dynamic in that learning and improvement can occur. The majority of our low-vision patients have visual loss secondary to some form of macular disease with normal functioning parafoveal retinal areas. We believe that it is this region of normal surrounding retina and the patient's ability to learn the use of eccentric viewing or fixation

which allows a higher level of functioning and performance. However, an exact determination of visual performance is a difficult task for which no rapid and simple test has been devised. It is hoped the Catford drum may be useful in evaluating this aspect. In our Low-Vision Clinic we are testing it as a means of estimating visual performance and the ability to learn the use of parafoveal retinal areas for vision.

Studies have been done comparing objective visual acuities with subjective measurements of visual acuities. These studies have used various methods of either inducing or arresting optokinetic nystagmus to determine measurements of objective acuity. A summary of these results reported by Pearson¹ shows that the correlation coefficient between objective and subjective measurement of visual acuity varied from +0.33 to +0.92. In defining the correlation coefficient linear regression techniques were used to minimise the sum of the squares of the deviations of the actual data points from the straight line of best fit. In particular, two studies concluded that there are differences in comparing results based on the visual

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acuity being tested. Wolin and Dillman² and Millodot *et al.*³ agreed that for a subject with relatively good acuity the subjective acuity is found to be slightly better than the measured objective acuity. However, the opposite is true for a patient with relatively poor visual acuity.

Catford and Oliver^{4,5} reported a good correlation in their results between Catford drum acuities and Snellen acuities in adults with visual acuities better than 6/60. The calculated correlation coefficient for that study is +0.87. Two studies have been published since then which directly compare the use of the Catford drum as an objective measurement of visual acuity with that of Snellen visual acuity. Atkinson *et al.*⁶ found that for emmetropes there was an overestimation of visual acuity with the Catford drum by a factor of approximately 4. For those individuals with reduced vision, either uncorrected myopes or emmetropes viewing through plus lenses to reduce acuity, the ratio between acuity measures involved an overestimation of Snellen acuities by a factor of at least 10. Khan *et al.*⁷ reported that eyes with relatively good vision, 20/50 or better, showed a good correlation between the subjective and objective acuities. However, there was poor correlation in eyes with 20/60 vision or less, in which case the objective acuities were generally better than the subjective acuities. Their calculated correlation coefficient was +0.61.

In summary, it appears that objective acuity measures correlate differently with subjective acuity measures depending on the method used. In dealing specifically with the Catford drum the evidence seems to indicate that the objective acuities as measured by the drum not only generally overestimate the subjective acuities, but do so by a factor which varies with the level of vision.

Materials and methods

The Catford drum (Fig. 1) was introduced by Catford and Oliver in 1971 as an instrument to determine visual acuity, especially in young children under 3 years of age, when reliable subjective responses cannot be elicited. It provides an objective method of determining visual acuity based on inducing an optokinetic nystagmus. The Catford drum consists of a motor driven drum with separated black dots of various sizes on a white background projected through a central aperture, measuring 4×6 cm. These dots can be rotated from left to right and back to the left again in a continuously repeating manner. The patient is seated the recommended 60 cm away from the Catford drum and is instructed to watch the selected dot with the eye to be tested. The visual acuity is determined by reducing the target size until

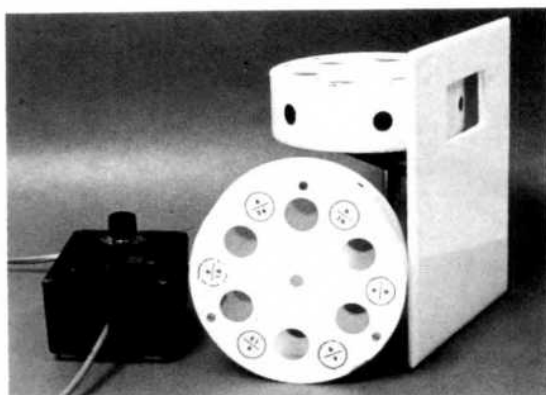


Fig. 1 The Catford drum apparatus.

the smallest dot is found which no longer produces a regular oscillatory eye movement (an optokinetic nystagmus). This endpoint is recorded and accepted as the objective equivalent to the Snellen visual acuity.

Catford and Oliver have calibrated the drum in terms of Snellen acuities from 20/20 to 20/600 based on the dot size at 60 cm, subtending an angle equal to the corresponding Snellen letter at 6 m. The speed of the rotating dot is controlled by a rheostat on an electrical transformer. This was adjusted to obtain the recommended setting allowing a full oscillatory cycle to repeat every one second.

Visual acuity was also measured by a standard Snellen chart projected on a screen at a distance of 6 m. All testing was performed with best spectacle correction. The same room was used for testing of all subjects to allow consistent and reproducible testing conditions. Recommended testing conditions for the Catford drum suggest its use in uniform bright daylight or equivalent artificial light. Uniform illumination was provided by ceiling based fluorescent lights. The luminance as measured at the central aperture of the Catford drum located 60 cm from the patient was 179 cd/m² as measured with a Spectra Pritchard photometer (Model 1980A-PL).

In the first part of the study patients in our Low-Vision Clinic were tested with the Catford drum at 60 cm as outlined above to determine objective visual acuity. The same eyes were then tested with the standard Snellen chart at 6 m to determine subjective visual acuity. The results were then compared. The patients had varying levels of subjective visual acuity from 20/30 to hand motion. In this half of the study only patients who recorded a visual acuity of 20/400 or better were accepted, since this is the upper limit of accuracy for the Snellen chart at 6 m. A total of 82 eyes were tested in this initial study.

In the second part of the study we wanted to assess

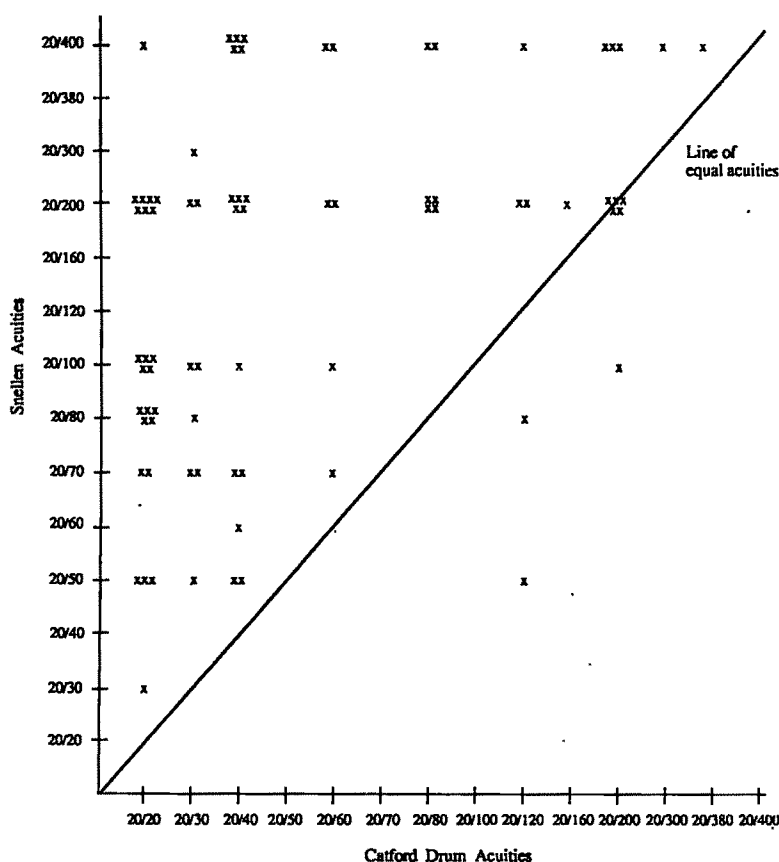


Fig. 2 Display of the Snellen visual acuity and the Catford drum acuity obtained for each eye tested on the initial visit. Each x represents one eye, with a total of 82 eyes tested.

visual performance as related to the patient's ability to learn the use of eccentric viewing or fixation with time. We scheduled testing of the low-vision patients with the Catford drum at 60 cm during the initial visit and on subsequent visits after one and six months of using standard low-vision aids. This consisted primarily of using high plus lenses from +5 dioptres to +32 dioptres based on the level of vision, along with basic instruction in low-vision principles. Low-vision aids are typically made for use with the eye that has the better visual acuity. Therefore testing of visual performance and the ability to learn eccentric viewing were evaluated with the patient's better eye, since there would be no training of the eye with the lower vision. Most patients in this clinic suffered loss of vision due to macular disease, usually secondary to age related macular degeneration and its sequelae. Patients who did not have any visual loss due in part to macular disease were excluded from this part of the study, since we were attempting to assess the ability to use eccentric viewing or parafoveal retinal areas for vision. A total of 15 patients were seen on

follow-up visits in the initial testing, all one month after initial low-vision instruction.

Results

Our findings based on 82 eyes indicated that visual acuities as measured by the Catford drum significantly overestimate the subjective acuities as taken by the Snellen chart. This overestimation occurred in all but eight eyes with 90.2%, or 74 out of 82 eyes tested, giving this result. 6.1% had equal visual acuities, and in 3.7% there was an underestimation of the subjective visual acuity by the Catford drum (Fig. 2). Therefore the great majority of the Snellen visual acuities recorded from 20/30 to 20/400 were overestimated by a factor ranging from 1.05 to 20.0, average 4.73. The most frequent overestimations of the Snellen visual acuity were by factors of 5 and 10, which occurred in 36% of eyes tested (Fig. 3). Factors were calculated from the visual acuity fractions, being converted to decimal equivalents and then compared with each other. Decimal notation is;

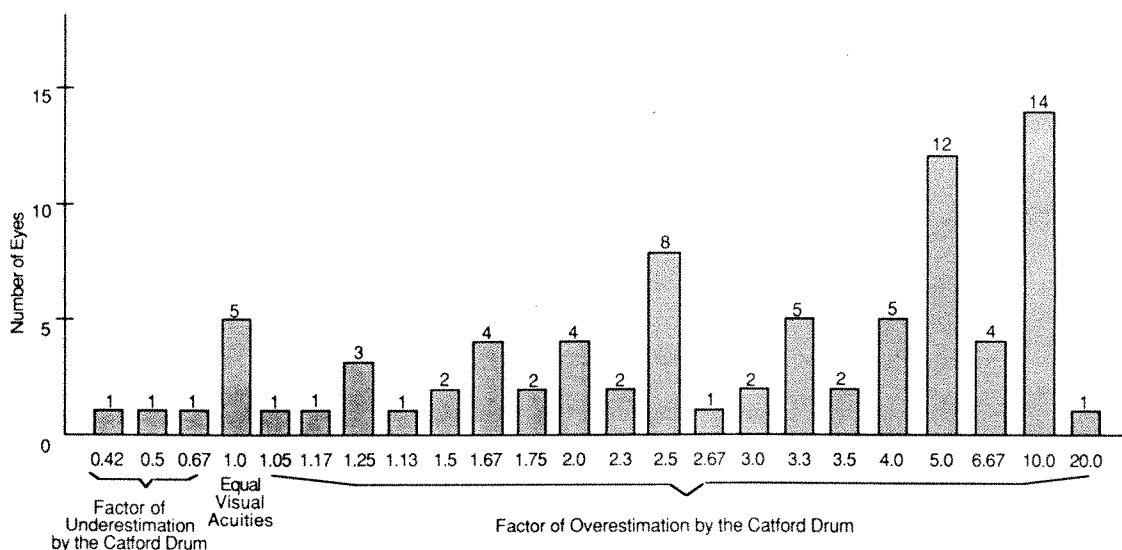


Fig. 3 Comparison of the Catford drum acuity with the Snellen acuity in each eye is done to obtain a factor of overestimation, underestimation, or equal visual acuity for each eye tested. The number of eyes with similar results is shown.

obtained by dividing the numerator by the denominator, and it is not a measure of the percentage of remaining vision or loss of vision. For example, 20/20 equals 1.0 and is an improvement by a factor of 5 over 20/100 with its decimal equivalent of 0.2. The calculated correlation coefficient for the study was +0.40.

In assessing visual performance as measured by the Catford drum in our low-vision patients we noted a considerable increase in Catford acuity, while the Snellen acuity remained without significant change during return visits. The results in 15 patients who were tested on follow-up visits one month after their initial low-vision instruction revealed that 12 out of the 15 patients (80.0%) showed an improvement in Catford acuity. Three of the patients tested showed no change in their Catford acuity after one month (Fig. 4). This improvement in Catford visual acuity was by a factor ranging from 0.3 to 10.0, average 4.08. Thirteen of the 15 patients showed no change in their visual acuity on repeat testing with the Snellen chart, with one patient improving one line and the other dropping one line on the Snellen chart. No data are yet available from longer term follow-up patients.

Discussion

The results of our study indicate that the Catford acuities almost uniformly overestimate those taken by the Snellen chart. Probably several factors explain this finding. Part of the reason for the overestimation of Snellen visual acuities may be the calibration of the

target sizes by Catford and Oliver. The diameter of the dot on the Catford drum was given a visual acuity which correlated with the overall size of the Snellen letter, with its designated visual acuity fraction. This was based on the fact that both the Catford dot and the Snellen letter subtend an equal angle at their viewed distance. Other investigators⁶ have pointed out the necessity of distinguishing between the 'minimum observable' object and the 'minimum separable' object. It is thought that the significant dimension of a Snellen letter for determining visual acuity is more likely the stroke width, which is 1/5 of the Snellen letter height. If this is accepted, it would result in an overestimation of the Snellen visual acuities by a factor of 5. An explanation for the poor correlation of results could in part be due to observer inaccuracy. Although the visual acuity determinations using the Catford drum were performed as Catford originally described, the ability to determine when an optokinetic nystagmus is present versus random eye movements may not always be accurately assessed by means of only visual methods of detection. However, other factors must be involved, since Khan *et al.*⁷ used electrical means of recording eye movements but still produced only a +0.61 correlation coefficient.

Our data result in a poor correlation between objective and subjective visual acuities, which differs from the results of Catford and Oliver. However, this finding is supported by the two other studies which have investigated the Catford drum, as mentioned

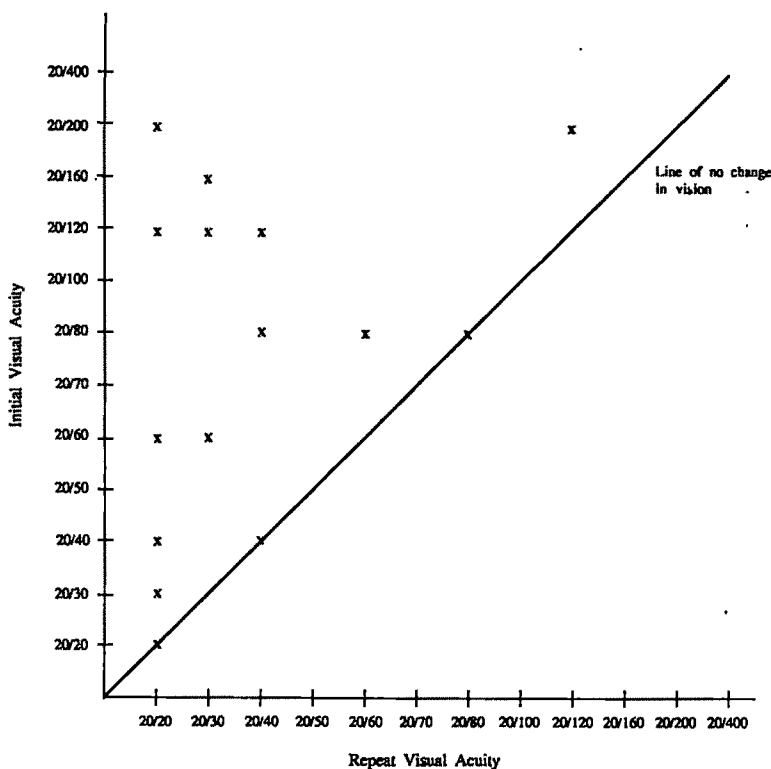


Fig. 4 Results of the Catford drum acuity on initial testing versus the Catford drum acuity obtained on one month follow-up visits. Each x represents one eye, with a total of 15 eyes tested.

earlier. The degree of overestimation by the Catford drum was noted to vary greatly with the level of vision being tested, and it is doubtful whether a recalibration of the Catford drum will be possible owing to the poor correlation of the data collected so far. For example, one patient had a Snellen acuity of 20/400 but had a 20/20 result with the Catford drum, while another patient had a Snellen acuity of 20/30 and a Catford acuity of 20/20.

Finally, it is not clear how the ability to pick out moving black dots of different specific sizes which in theory are supposed to be equivalent to a corresponding Snellen letter correlates as a test of resolution. It would seem other factors must be involved, such as contrast sensitivity, motion detection and others.

In the second part of the study another method of visual acuity testing, the Catford drum, was used to test our theory that low-vision patients develop new skills that allow them to perform better than expected from traditional visual acuity measurements. The results show that the Snellen visual acuities did remain stable, as expected, in contrast to the Catford acuities, which improved on follow-up visits. Since this increase in Catford acuity cannot be explained on the basis of an improvement in the underlying

disease, other processes must be involved, such as learning to use eccentric areas for vision.

This conclusion is given support by a recent report from Harris *et al.* at the Wilmer Ophthalmological Institute. They report that patients with macular disease do not spontaneously use their best eccentric area of retina for vision. Furthermore, they report 90% of their patients were able to show a two- to four-fold improvement in visual acuity when eccentric or parafoveal areas were specifically tested. They conclude: 'training of fixation behaviour to favour eccentric areas of retina ... may prove valuable in visual rehabilitation.' This is a view we have shared in our clinic for a long time and for which the above data lend further support in our opinion. The time course during which the improvement takes place suggests there is an 'adaptation or learning phenomenon' occurring.

A major factor in this adaptation process might be the fact that our patients are becoming more skilful in the use of eccentric or parafoveal retinal areas with the help of low-vision aids and instruction. This is compatible with the fact that we have noticed that in patients with very large central scotomas the improvement in performance is less and takes longer than in patients with smaller central scotomas. In our

study three of the 15 patients seen on their initial follow-up after one month of training showed no improvement in the Catford visual acuity. These results might be explained by the extent of the patients' macular disease. If they had developed a larger area of macular involvement this would result in a larger central scotoma. Therefore one could theorise that these patients might require more practice and skills to be able to locate and develop the use of these parafoveal areas found at greater distances from the fovea. It would be interesting to review the fundus findings and compare visual fields in these patients to determine if larger central scotomas were present. In addition other factors almost certainly play an important part in the ability and rate of learning to use parafoveal retinal areas. For example, the patient's psychological state, influenced by the loss of a loved one or denial of their eye disease, can significantly delay this learning process from our past experiences with these patients. We expect these three patients will most likely show improvement with time. We await further follow-up visits on these patients and others for further confirmation of our initial findings.

In summary, we consider most low-vision patients function at a higher level than would be predicted from their Snellen visual acuity. This seems to be based on their ability to learn the use of eccentric viewing, in other words their ability to use a parafoveal retinal area which has a better capacity for useful vision than their damaged fovea. Our current methods of assessing low-vision patients with the Snellen chart are inadequate. 67% or 55 out of 82 eyes tested had a visual acuity of 20/100 or less. This makes the Snellen chart a poor choice for examining

low-vision patients owing to its unreliability and lack of accuracy at that level of vision. It is obvious that other techniques must be tried, such as the 'full field E' visual acuity test of Harris *et al.*,⁹ the Snellen chart at 5 feet (1.5 m), etc. The Catford drum may be a starting point in helping to assess better the visual performance and the true visual potential of low-vision patients.

We are continuing our study and will report further data later, but we hope this report will enable our fellow ophthalmologists to use this information to their patients' benefit and to initiate similar studies to test the validity of our observations.

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Obituary

Frank William Law, MA, MD, BChir, FRCS, LRCP

Frank Law died on 26 May 1987 at his home in Chipperfield aged 88 years. He was born in Isleworth on 12 August 1898 and was educated at St Paul's School and later at St John's College, Cambridge. He qualified in 1926 with the degree of MB, BChir, having completed his undergraduate training at the Middlesex Hospital. His medical studies were interrupted by the first world war, during which he served in the Royal Artillery in France and Flanders.

After deciding to specialise in ophthalmology he became at first house surgeon and then the senior resident officer at Moorfields Eye Hospital, where in 1936 he was appointed honorary surgeon. He was also appointed honorary ophthalmic surgeon to Guy's Hospital. With the formation of the National Health Service in 1948 these appointments were automatically renamed consultant surgeon. He was also consultant ophthalmic surgeon to the King Edward VII Hospital for Officers, and civilian ophthalmic consultant to the Army.

Frank Law was also a Knight of the Order of St John and was closely associated with the Order's Eye Hospital in Jerusalem. He was actively engaged in many ophthalmic congresses. In 1950 he was secretary general of the International Ophthalmological Congress held in London. This was an outstanding success despite the many difficulties occasioned by the shortages of almost everything in postwar Britain. He was president of the Faculty of Ophthalmologists and a long-term member of the Oxford Ophthalmological Congress, of which he was master for two years. He was a very active serving member of the Ophthalmological Society of the United Kingdom, being honorary secretary for eight years and honorary treasurer for 33. Even during his two years as president of the society he continued as treasurer. He did much to foster co-operation between ophthalmologists and opticians and was a member and master of the Worshipful Company of Spectacle Makers. He was awarded an honorary FBOA. He also travelled widely in the course of his profession and was an honorary member of many overseas ophthalmological societies. He was an enthusiastic teacher of undergraduate and postgraduate students both at home and abroad. In this connection he was appointed honorary visiting ophthalmologist at Johns Hopkins Hospital, Baltimore. In his later years he became interested in the history of British ophthalmology and wrote books on the history of Moorfields Eye Hospital, of the Ophthalmological Society of the United Kingdom, and of the Worshipful Company of Spectacle Makers.

It might be imagined that in view of such extensive commitment to ophthalmology that Frank Law would have little time for other activities. However, this was not the case. He was devoted to music and played the piano and organ excellently. In quiet moments he would also engage in meticulous embroidery work. He had a wide knowledge of heraldry and was associated with the formation of the coats of arms of the OSUK and the Faculty of Ophthalmologists.



His greatest hobbies were, however, in the field of sport. At Cambridge University he was captain of the Lady Margaret Boat Club and rowed at number 2 in the University Boat Race of 1923. He retained a close interest in rowing throughout his life, being a member of the Leander Club, and he always attended the Henley Regatta. He was accomplished at Royal Tennis, and as a member of the MCC he played at least weekly at their courts at Lords. He was a very sound shot and went regularly to Roxburghshire in the grouse and pheasant seasons. He could also be found at dawn in winter wild fowling on the Solway Firth. He greatly enjoyed trout and salmon fishing, and it was a delight to be with him on the river bank in places as far apart as Hampshire, Hereford, and Aberdeenshire. Not only did he cast his fly to perfection but his knowledge of the wild life around added enormously to the interest. His anecdotes and ready wit could also transform an otherwise unrewarding day into a memorable one.

There must be hundreds whose lives have been enriched by knowing Frank. Particularly endearing was his readiness to help a colleague, especially a younger one. However busy he might be, he was never too busy to listen. Despite having achieved great success and indeed fame he was above all, in the words of his favourite author Thomas Hardy, 'A good man and he did good things'. He is survived by his wife Brenda (Tommy) to whom he was married for 58 years, and by his son and daughter.

DA

Book review

The Retina: A Model for Cell Biology Studies. Part 1. Eds. Ruben Adler and Debora Farber. Pp. 363. £44.00. Academic Press: Orlando, Florida. 1986.

Given the current expansion in terms of biological journals and in particular journals which cater for review articles, it is extremely difficult to define the role of books such as this. It is certainly not a book for the student of ophthalmology or for the medical student who wishes to learn about this particular system of the eye.

The book is obviously written for the specialist. The problem is which specialist. The book contains eight reviews, most of them extremely well written by leading authorities. What it lacks is the logic and guidance of a single editor. It resembles to some extent the sort of volumes that we are now used to seeing as a result of obscure meetings in even more obscure locations. All the scientific authors should consider the goal of their work before embarking on exercises of this kind.

Having been less than kind to the framework and concept

of this sort of volume I think the individual contributions are on occasion well worth reading by the hyperspecialist. Of particular interest are the chapters by C C Getch and M S Steinberg on 'Differential adhesion in neuronal development' and the chapter by J C Besharse on 'Photo-sensitive membrane turnover: differentiated membrane domains and cell-cell interaction.' Both these contributions give the reader an up-to-date review of their respective areas while at the same time presenting complex material in an eminently readable form. Other contributions unfortunately do not achieve this standard, and some degenerate into the obscure nomenclature of the hyper hyperspecialist.

In essence some chapters of this book will be extremely helpful to some people. However, very few will find the whole book of relevance. I can imagine this having a limited shelf life and would have preferred the contributions to be made to journals rather than to be reproduced as such a disjointed single volume.

JOHN MARSHALL

Notes

Ocular trauma

An International Congress on Ocular Trauma will take place in Tel-Aviv, Israel, on 19-24 February 1989. Further information from the Secretariat, International Congress on Ocular Trauma, PO Box 50006, Tel-Aviv 61500, Israel.

Royal Eye Hospital poster prize

A prize of £200 and a certificate will be awarded to the best poster presented at the Annual Congress of the Ophthalmological Society of the United Kingdom in

Harrogate, 20-22 April 1988. The prize will be allocated on the quality of the poster as well as on the way the presenter discusses his/her poster with the judges. It is therefore essential that the author is available at the meeting to present the poster in person. The first author of the poster presented must be under the age of 40 years at the time of the meeting, although there may be collaboration with older workers who may be named on the poster. The presentation of the prize will be made by the president at the annual dinner of the Society during the Annual Congress. Further details from the Honorary Secretary, OSUK, Bramber Court, 2 Bramber Road, London W14 9PQ.

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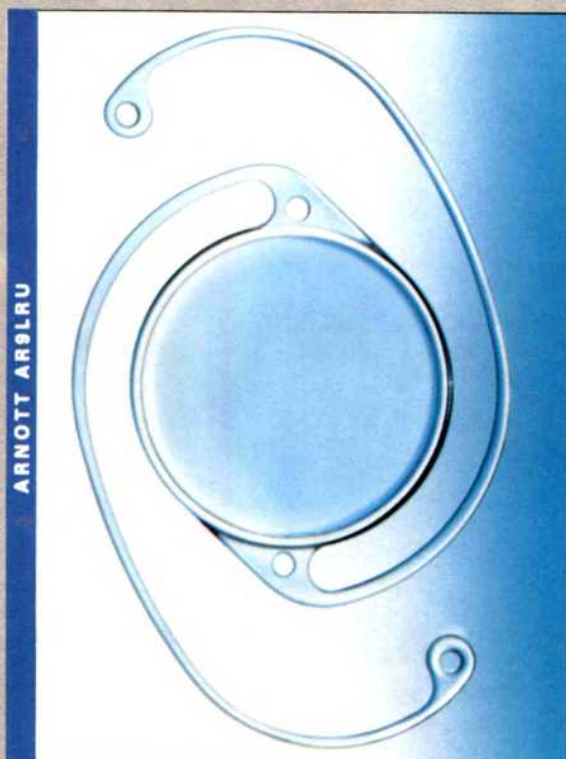
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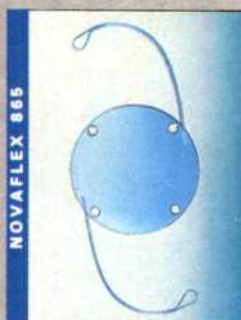
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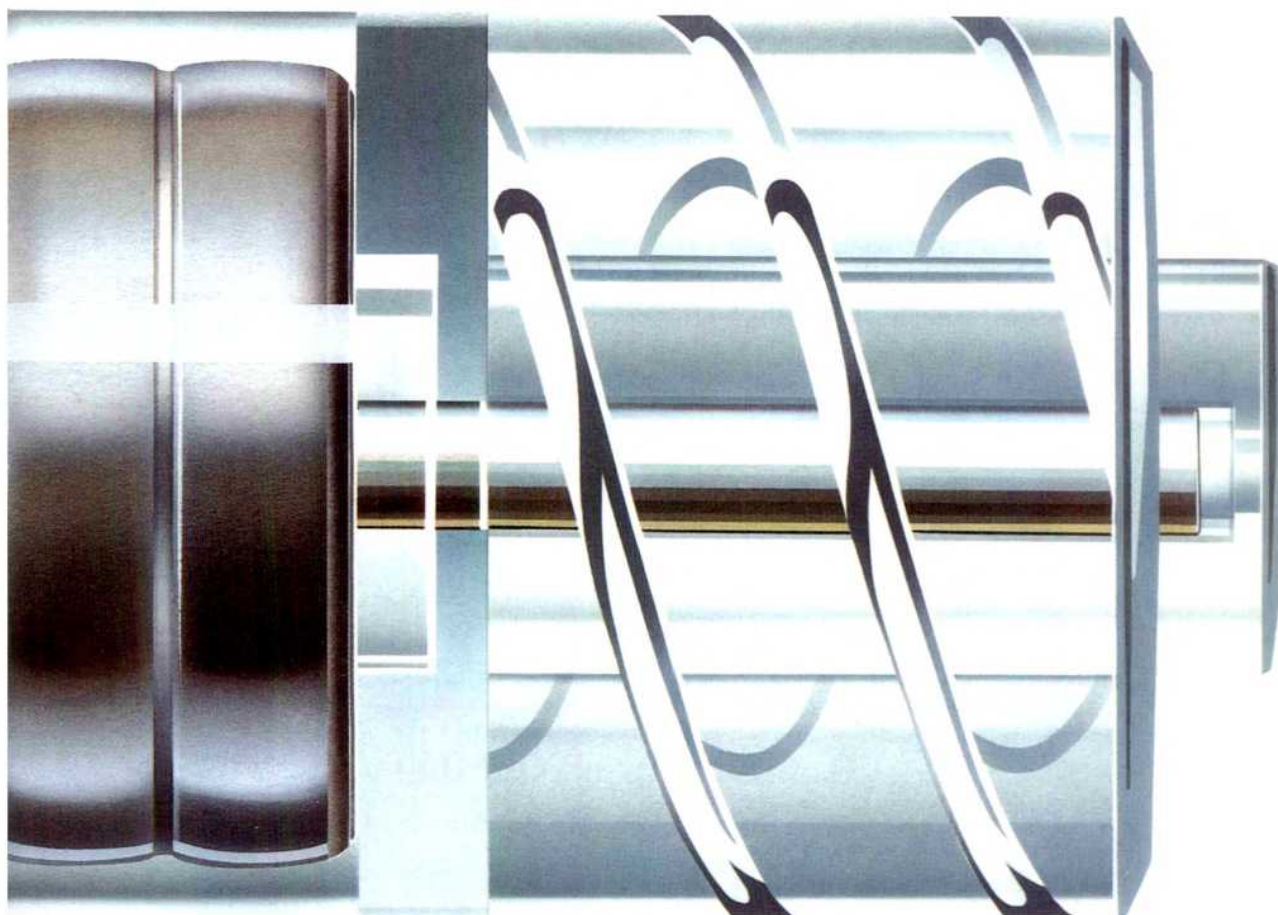
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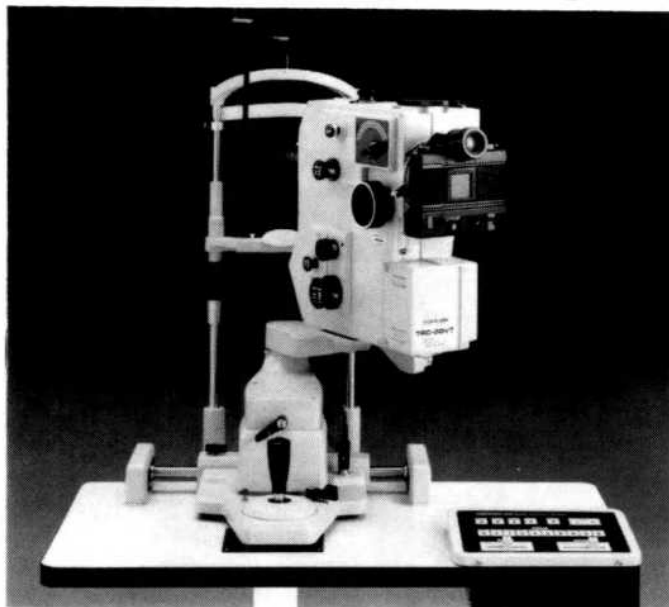
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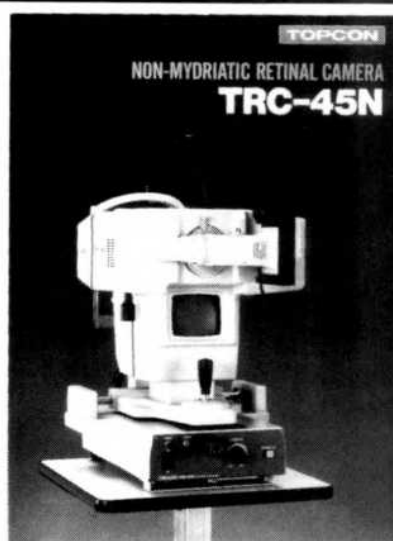
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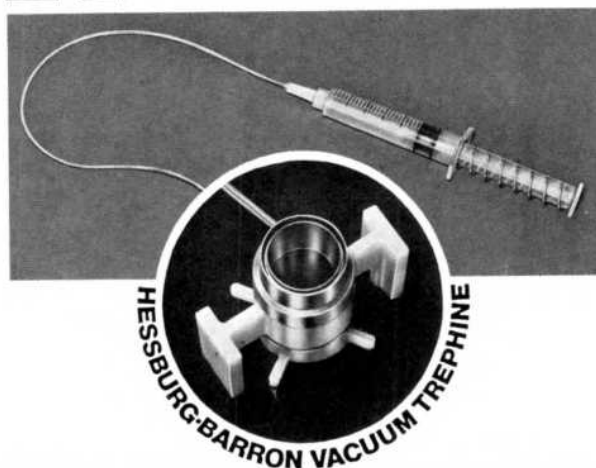
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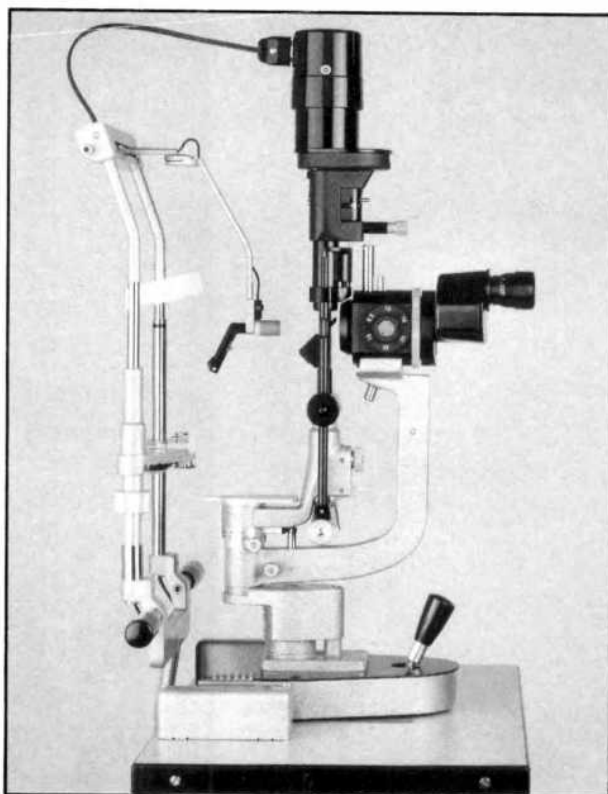
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Editorial: Herpes zoster ophthalmicus and AIDS

AIDS is a new disease, first described in 1981,¹ of obscure origin, most likely from Africa, which is rapidly establishing itself throughout the world. It has many parallels with the early days of syphilis in that it has allegedly been imported by travellers from a little-known continent, is mainly spread by sexual promiscuity, and is a multisystem disease that is untreatable, leading inexorably to insanity and death. The causative agent has been identified as a retrovirus now called HIV (formerly HTLV III). It was first described in a small group of young adult American male homosexuals with pneumocystis pneumonia and Kaposi's sarcoma, with a proclivity for opportunistic infections. The ophthalmologist tends to see the disease in its later stages, when the typical retinal changes of the opportunistic infections occur, namely cytomegalovirus, toxoplasmosis, candidiasis, and other fungal infections. Cotton-wool spots are perhaps the commonest manifestation and are probably due to early cytomegalovirus infection.² Sadly most patients die shortly after referral to the ophthalmologist despite vigorous efforts to treat their infections.

The number of patients with positive serology for HIV is expanding considerably in central Africa, and figures as high as 20% have been quoted on random testing.³ There has been some controversy over why this is so. Some say it is due to reusing contaminated needles and syringes in these communities,⁴ but the majority that it is due to heterosexual promiscuity.⁵

The disease has a very long incubation period of four years and more. Furthermore, many patients may show positive ELISA testing and be asymptomatic (pre-AIDS). It is not known what will happen to this group of patients. Some we know go on to persistent generalised lymphadenopathy and florid AIDS, but as for the rest time alone will tell. Very early cases of AIDS have been described as showing herpes simplex, herpes zoster, and tuberculosis.^{6,7}

Herpes zoster on the other hand is an old disease, well known in antiquity, and, although common in Western countries among older people, it has formerly been seen sporadically in Africa. Most herpes zoster occurs in healthy people, though a very small proportion of cases are in younger, immunocompromised patients (systemic zoster).⁸ In these cases the rash will often spread to the rest of the body, the pain and complications tend to be more severe, and the response to intravenous acyclovir is better.⁹

In this issue of the *BJO* a number of cases are reported of young apparently fit patients with herpes zoster ophthalmicus and positive ELISA tests for HIV. A further interesting finding is peripheral retinal perivasculitis and sheathing. Although this is well described pathologically in ophthalmic zoster, it is rarely seen clinically. The rash and ocular complications are described as more severe than usual in this group of patients, though it must be said that the group of patients compared against them were not in any way comparable. It must remain a matter of opinion, but it may be questioned whether the ocular complications were adequately treated with topical steroids.

The position of acyclovir, whether topically, orally, or intravenously in these patients, is rather unsure. It is difficult to achieve adequate safe therapeutic blood levels, and the drug is expensive, especially for routine use in the Third World.

While it is clearly neither practical nor appropriate to check for HIV in every patient with ophthalmic zoster under the age of 40, we must bear it in mind when examining vulnerable groups of patients in this country, namely, promiscuous homosexuals (and now heterosexuals) and intravenous drug abusers.

RJM

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Severe herpes zoster ophthalmicus in young African adults: a marker for HTLV-III seropositivity

P KESTELYN, A M STEVENS, E BAKKERS, D ROUVROY,
AND P VAN DE PERRE

From the Centre Hospitalier de Kigali, Rwanda

SUMMARY This report proves the relationship between herpes zoster ophthalmicus and seropositivity for HTLV-III in young and often apparently healthy African patients. The ophthalmologist should screen patients with herpes zoster ophthalmicus for antibodies against HTLV-III in areas where this virus is endemic or if the patient belongs to a known risk group. If the test is positive, the patient should be instructed about the infectious nature of his condition to prevent spread of this sexually transmitted disease. As the rate of corneal involvement and postherpetic neuralgia are very high in these patients, it would be worthwhile to ascertain whether routine use of acyclovir treatment in HTLV-III seropositive patients with herpes zoster has a beneficial effect on these complications.

It is well known that herpes zoster infections occur with greater frequency in immunocompromised patients.¹ Since the first description of HTLV-III infection in Rwanda in 1984,² the number of cases of herpes zoster ophthalmicus (HZO) seen in our ophthalmology department at the Centre Hospitalier de Kigali has been steadily increasing. The purpose of the present study was twofold. First we wanted to determine whether there is a relationship between this increasing frequency of HZO and the presence of HTLV-III in the population. Secondly we wanted to document the degree of eye damage caused by this herpetic infection.

Material and methods

All patients with HZO followed up in our department between September 1985 and February 1986 were tested for antibodies against HTLV-III with a commercial ELISA kit (Vironostica Organon Teknika BV Boxtel Holland), as recommended by the World Health Organisation (Bangui Conference, 22–23 October 1985). Positive tests were confirmed by an indirect immunofluorescence method using HTLV-III infected H9 fixed cells and uninfected H9 cells as an internal control.³ In addition to the routine ocular examination, including visual acuity testing, slit-lamp examination, and funduscopy, a standard

questionnaire was completed giving information about the patient's geographic origin (prefecture), his residency (urban versus rural), first date of diagnosis, involvement of one or more dermatomes, duration of the healing period, and presence or absence of postzonal neuralgia. Whenever possible the patients were examined at weekly intervals until healing or stabilisation of their infection took place. HTLV-III antibodies were also determined in a control group matched for age, sex, geographic origin, and residency. This control group was recruited from healthy blood donors; three controls were taken for each patient with HZO.

Results

In this five-month period we diagnosed 19 cases of HZO in 15 male and four female patients. In 17 patients a typical skin eruption was present on the nose (nasociliary nerve) and on the forehead (frontal nerve). In two patients (cases 12 and 19) the eruption was mainly located on the cheek (branches of the maxillary division of the fifth nerve), but there was mild involvement of the frontal and nasociliary nerves as well. Although the skin lesions were often deep and healed with conspicuous scar formation, there were no instances of permanent functional damage to the eyelids. The age of the patients varied between 19 and 46 years (mean 29 years, median 28 years). Two of them complained of weight loss and

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lassitude (patients 3 and 6). Patient 6 reported a history of right facial palsy and a vesicular eruption of the right ear one year ago, most probably a Ramsay Hunt syndrome, due to herpes zoster of the geniculate ganglion. Patient 7 reported an episode of thoracic herpes zoster in August 1984. The other patients declared themselves to be in good general health; they had no clinical evidence of malignant disease and none of them had recently been in hospital.

The healing period of the ocular involvement in these 19 patients varied between three weeks and five months (median one month). Eight out of 19 (42%) still felt some pain in the orbital region, though the skin and eye lesions had cleared.

SEROLOGICAL RESULTS

All these patients with HZO had antibodies against HTLV-III (100%). In the control group only seven out of 57 patients were seropositive (12.2%). Fisher's exact test: $p=0.001$.

OPHTHALMOLOGICAL FINDINGS

Table 1 summarises the ophthalmological findings in these 19 patients. The corneal complications were described in accordance with the terminology used by Liesegang.⁴ Seventeen patients (89.4%) showed some form of corneal involvement, ranging in severity from a mild punctate epithelial keratitis to a vision-threatening corneal oedema. Only the two patients with predominant involvement of the maxillary nerve did not have corneal complications.

Uveitis was seen in 10 out of 19 patients (52.6%), with posterior synechiae in three of them.

Eleven of the 19 patients (57.8%) suffered from a decrease in visual acuity attributable to the sequelae of their zoster infection. In six patients (cases 8, 9, 11, 15, 16, and 17) there was a drop in visual acuity due to the formation of central nummular corneal scars. Two patients (cases 1 and 10) developed a serpiginous ulceration which resulted in corneal thinning and irregular astigmatism and a more pronounced decrease in visual acuity. Patient 3 had peripheral neovascularisation of the cornea, central nummular scars, and some degree of corneal oedema. The visual acuity of patient 4 was reduced to 6/60 as a result of chronic corneal oedema. This patient had a prolonged illness and suffered from keratouveitis and endotheliitis. After seven weeks of illness he was treated with intravenous acyclovir 30 mg/kg for seven days, with improvement of his clinical state. Vasculitis with anterior segment ischaemia led to a thickened oedematous cornea and a white limbus surrounded by dilated vessels, much as is seen after an extensive corneal burn. This was the only patient treated with intravenous acyclovir. All other patients received a combination of cycloplegic drugs (atropine 1%) and oxytetracycline 1% and hydrocortisone 0.5% ointment. The atropine was prescribed twice daily until flare and cells had completely disappeared. The ointment was prescribed from twice to six times daily depending on the severity of the ocular involvement, and it was continued until the eye became white.

Table 1 Ocular complications in 19 patients with HZO

No.	Age	Sex	VA	Ocular involvement	Duration	Sequelae
1	33	M	6/15	EP, ASI, SU, uveitis	5M	Peripheral+central NCS, astigmatism
2	26	M	6/6	EP, ASI	5M	Peripheral NCS
3	32	M	6/15	EP, ASI	3M	Central+peripheral NCS, neovascularisation Deep interstitial oedema
4	34	M	6/60	EP, ASI, keratouveitis, endotheliitis	2M	Chronic corneal oedema, posterior synechia
5	27	M	6/6	EP, uveitis	6W	None
6	29	M	6/6	EP, ASI	1M	Peripheral NCS
7	36	M	6/7.5	EP, ASI	3W	Peripheral NCS
8	20	M	6/10	Central ASI, uveitis	1M	Central NCS
9	34	M	6/8.6	ASI, uveitis	1M	Central+peripheral NCS
10	25	M	6/15	EP, SU, uveitis	2M	Corneal thinning, neovascularisation, Astigmatism, posterior synechia
11	19	F	6/12	PEK, ASI, uveitis	1M	Central+peripheral NCS, posterior synechiae
12	28	M	6/6	None	3W	None
13	24	F	6/6	EP, PEK, uveitis	3W	Peripheral NCS
14	25	F	6/6	PEK	1M	None
15	25	M	6/12	ASI, uveitis	6W	Central+peripheral NCS
16	46	M	6/15	EP, PEK	1M	Central NCS
17	22	M	6/10	ASI, uveitis	1M	Central+peripheral NCS
18	31	F	6/6	ASI	3W	None
19	34	M	6/6	None	3W	None

VA=visual acuity. Duration: M=months, W=weeks. EP=early pseudodendrites. PEK=punctate epithelial keratitis. ASI=anterior stromal infiltrates. SU=serpiginous ulceration. NCS=nummular corneal scars.

Fundus lesions which we considered to be unrelated to the actual attack of herpes zoster were observed in six patients. The fundus of the right eye (contralateral to the herpes zoster infection) of patient 2 showed a heavy perivasculitis of the peripheral vessels and a moderate degree of vitreous flare. Five other patients (cases 6, 11, 13, 17, and 18) had bilateral perivasculitis of the peripheral retinal vessels, varying from a discrete perivascular sheathing to a frank perivascular infiltrate.

Discussion

The most striking finding in this study is that all our patients with HZO are HTLV-III seropositive. This statistically highly significant association amply confirms our clinical impression that there is a relationship between the rising number of cases of HZO and the advent of HTLV-III infections in Rwanda. As already suggested by Cole and coworkers,⁵ acquired immune deficiency syndrome (AIDS) should be considered in young, healthy persons with HZO and no known cause of immunosuppression. They described HZO in four patients, two with AIDS and two with the AIDS related complex. Our series of HZO adds an important aspect to their observation: HZO is not only a manifestation seen in patients with AIDS or AIDS-related complex, but also a marker for HTLV-III seropositivity in healthy carriers. Indeed 17 of 19 seropositive patients with HZO (89.4%) affirmed themselves to be in good health. They had no lymphadenopathy and they did not complain of weight loss, fatigue, night sweats, or diarrhoea. The clinical features of herpes zoster ophthalmicus in HTLV-III positive patients are somewhat different from the classical picture of this disease. In our opinion two distinct differences should be stressed. First, the peak incidence of HTLV-III related HZO is situated in a young age group (third decade), and, secondly, the disease tends to run a more severe course in HTLV-III positive patients in terms of corneal involvement and postzonal pain. Table 2 illustrates these differences by comparing selected clinical features of our

patients with a series published by Womack and Liesegang.⁶ The rates of corneal involvement and of postherpetic neuralgia are much higher in our series of HTLV-III seropositive patients. Similar conclusions are reached by Sandor and coworkers,⁷ who state that HZO occurs with frequent ocular complications in a subgroup of adults distinguishable by their young age and the presence of AIDS-risk factors.

We believe from the present study that the laboratory investigation of patients with herpes zoster should include a determination of antibodies against HTLV-III in areas where this virus is endemic or in patients with known risk factors. The presence of a perivasculitis or perivascular sheathing of the peripheral fundus vessels in both eyes may already give a clue to the presence of HTLV-III infection in a case of HZO. We described this finding in patients with AIDS and AIDS-related complex, both in children and in adults,^{8,9} and observed it in five patients of the present series. The ophthalmologist should inform the seropositive patient that he is a potential source of infection for his sexual partners and refer him to a venereologist for further counselling on this subject.

The high percentage of corneal involvement with subsequent visual loss and of postzonal neuralgia in this group of patients seems to justify the routine use of intravenous acyclovir, the current treatment of choice for zoster infections in immunocompromised patients.¹⁰ Unfortunately this treatment is far too expensive for routine use in a developing country. In our patients we were reluctant to give large doses of steroids for several reasons. Systemic treatment with steroids, advocated for severe cases of HZO and postherpetic neuralgia,^{11,12} is in our opinion contraindicated in HTLV-III seropositive patients, especially in Africa, where follow-up is less than optimal and where complications of systemic steroid treatment may cause more harm than the loss of visual acuity in one eye. Topical prednisone treatment should be used sparingly in the presence of epithelial disease,⁴ and a high number of our HTLV-III seropositive patients presented with early pseudodendrites and punctate epithelial keratitis (see Table 1), indicating active viral replication with the corneal epithelium. Although we agree that the visual outcome in some of our cases was negatively influenced by the withholding of potent topical steroids, it should be kept in mind that, once instituted, steroids need to be given over a long period, as later recrudescences are especially common after corticosteroid withdrawal. This means placing a heavy financial burden on our mostly poor patients.

Further follow-up of our HTLV-III seropositive patients with HZO but in good general health will tell whether they are at greater risk for developing AIDS

Table 2 Comparison of selected clinical features in two groups of patients with HZO

	Our series	Womack and Liesegang ⁶
Number of patients	19	86
Mean age	28 years	65 years
Ocular involvement	17 (89.4%)	61 (70.9%)
Corneal involvement	17 (89.4%)	47 (54.6%)
Uveitis	10 (52.6%)	37 (43%)
Substantial visual loss (6/15 or less)	5 (26.3%)	24 (28%)
Postherpetic neuralgia	8 (42%)	15 (17.4%)

or the AIDS-related complex than a seropositive group without a history of herpes zoster.

Addendum. In the period between March 1986 and September 1986 we diagnosed 21 new cases of HZO at our ophthalmology department. All but one patient had antibodies against HTLV-III. The one seronegative patient was a 55-year-old expatriate.

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Treatment of CMV retinitis in an AIDS patient

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SUMMARY We present a case of cytomegalovirus (CMV) retinitis in an AIDS patient who survived for 10 months after the start of his ocular problems. The retinitis responded to dihydroxy propoxy methyl guanine (DHPG) but relapsed four to six weeks after each course of treatment with progressive retinal destruction. One relapse was therefore treated with trisodium phosphoformate hexahydrate (Foscarnet). There are few reports of the use of this drug in the treatment of CMV retinitis with AIDS, but it appeared to be less effective in our patient than DHPG, possibly because of poor penetration of the blood-ocular barrier. A final course of outpatient maintenance therapy with DHPG failed to prevent a preterminal relapse of the retinitis. Fundus photographs demonstrated the resolution and relapse of the retinitis associated with each course of treatment. Maintenance therapy with DHPG would appear to be necessary to prevent relapse, but the logistics of this are difficult, and the effective dosage of DHPG is as yet uncertain.

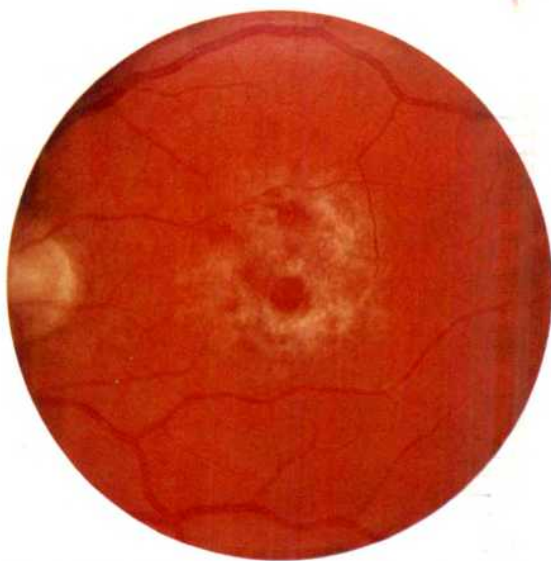
Patients with acquired immune deficiency syndrome are commonly found to have ocular lesions. Cotton-wool spots, isolated retinal haemorrhages, conjunctival Kaposi's sarcoma, and cytomegalovirus (CMV) retinitis have been widely described.¹⁻⁴ Other opportunistic infections occur less frequently and include cryptococcosis, toxoplasmosis, atypical mycobacterial infection, herpes simplex retinitis, and herpes zoster ophthalmicus.⁴⁻⁷ In a large series of eyes taken at necropsy from 35 consecutive AIDS patients CMV retinitis was the commonest infection, being found in 12 cases (18 eyes, 34%).⁸

The clinical features of CMV retinitis in AIDS are of progressive retinal destruction with fluffy white retinal infiltrates and intraretinal haemorrhages, often most marked along the major retinal vessels. Histologically there is full-thickness retinal necrosis with intracellular and intracytoplasmic inclusions. Virions may be identified on electron microscopy and virus antigen on indirect immunofluorescence. In AIDS it is not practical to confirm the diagnosis by obtaining intraocular specimens but the clinical diagnosis is supported by demonstrating cellular immune deficiency and human immunodeficiency virus (HIV, and also known as HTLV III/LAV) antibody in association with positive CMV serology or virus isolation from blood, urine, and secretions.⁹

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Pepose *et al.*⁸ have drawn attention to the frequent development of CMV retinitis in those AIDS patients with cotton-wool spots and propose that the cotton-wool spots are a manifestation of an immune complex mediated microvasculopathy which allows cell-free and cell-associated cytomegalovirus to infect the retina by traversing damaged retinal endothelial cells. They also distinguish between a non-inflammatory cytomegalovirus retinopathy seen in patients without AIDS and the cytomegalovirus retinitis seen in many patients with AIDS. In those with AIDS neutrophil function is preserved and may play a part in the progressive retinal necrosis of CMV retinitis. By contrast, infants, graft recipients, and patients with malignant disease often have defective neutrophil function, and when they develop disseminated CMV infection the retinopathy is less severe.

Experience of the specific treatment of disseminated CMV infection is limited, but over the past year remission of CMV pneumonitis, colitis, and retinitis in patients with immunodeficiency due to AIDS, allografts, and lymphoreticular neoplasms has been reported after administration of 9-(1,3-dihydroxy-2-propoxymethyl) guanine (DHPG, Syntex Research) and of trisodium phosphoformate hexahydrate (Foscarnet, Astra Pharmaceuticals). DHPG is also known as BW B759U (Burroughs Wellcome). We report our experience of the use of



Figs. 1-7 Fundus photographs of the left macula and superotemporal retina demonstrate the retinopathy and effects of treatment and relapse.

Fig. 1 Fresh retinal infiltrates and haemorrhages at the macula before treatment.

both these agents in the treatment of one AIDS patient with relapsing CMV retinitis.

Case report

A 47-year-old male homosexual presented to the Eye Department in June 1985 with left visual loss. Seven weeks previously he had been treated with high-dose co-trimoxazole because of an atypical pneumonia presumed to be due to *Pneumocystis carinii* and at that time HIV antibody was demonstrated in the serum.

At presentation the right visual acuity was 6/5, N5, and the left was 6/36, N12. He read all the Ishihara colour plates correctly on the right and made four errors on the left. The eyes were white, and the anterior chambers were quiet. The right visual field, vitreous, and fundus was entirely normal. There was a dense central scotoma on the left side with a clearly demarcated 2-disc diameter area of intraretinal haemorrhages and white infiltrates at the macula. There were no cells in the left vitreous.

In July he developed oropharyngeal candidiasis and nystatin lozenges were prescribed. In late August the left visual acuity deteriorated to counting fingers, and fresh retinal lesions were seen (Fig. 1, 29 August 1985). A clinical diagnosis of CMV retinitis was made and dihydroxy propoxy methyl guanine (DHPG, Syntex Research) 10 mg/kg/day was administered for

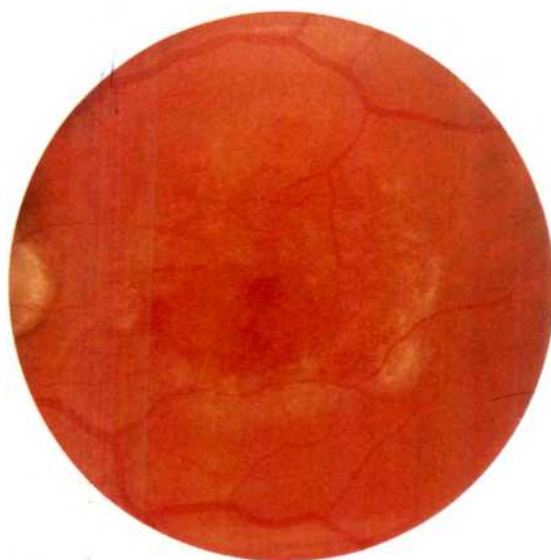


Fig 2A

Figs. 2A, B Good resolution of the retinitis after the first course of treatment with DHPG.

21 days. The retinitis improved without change in the visual acuity (Figs. 2A, B, 9 October 1985). The patient felt better and his weight improved. No systemic side effects of treatment were observed. The white cell count and neutrophil count remained normal at $5.8 \times 10^9/l$ and $2.9 \times 10^9/l$ respectively, but there was a persistent absolute lymphopenia of below $1.0 \times 10^9/l$. He developed oesophageal candidiasis,

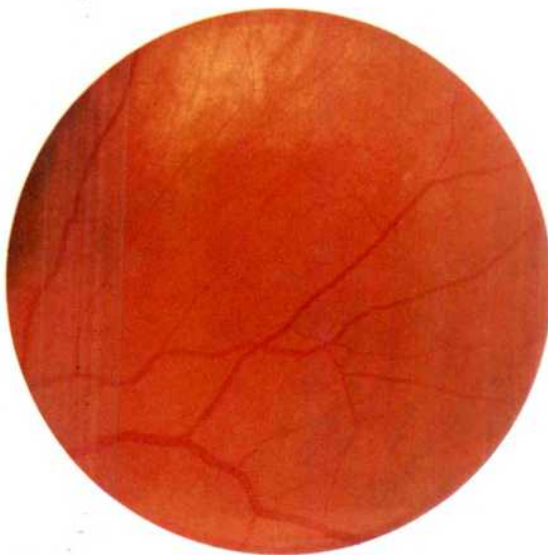


Fig. 2B

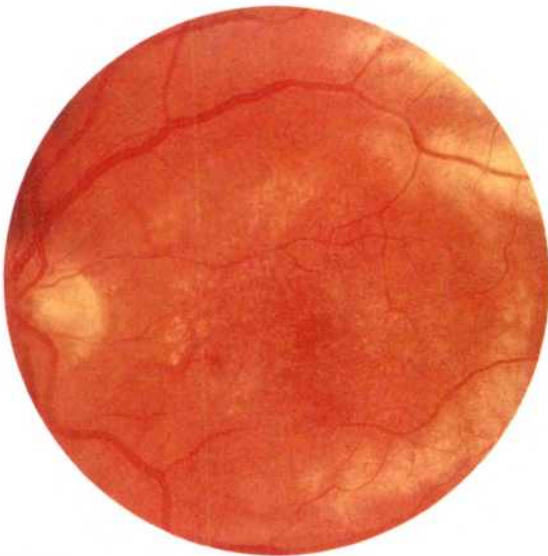


Fig. 3A

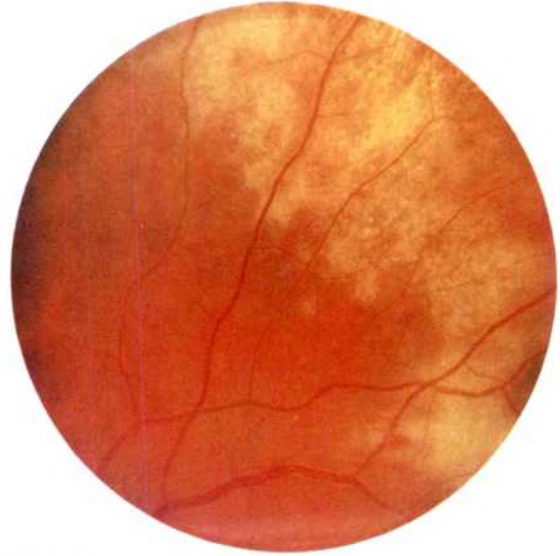


Fig. 3B

Figs. 3A, B *Relapse and further retinal destruction in adjacent viable retina six weeks later.*

which was treated with ketoconazole 200 mg once daily.

Six weeks later, in November 1985, the right visual acuity fell to 6/36, and fresh lesions consistent with CMV retinitis were seen in both eyes (Figs. 3A, B, 25 November 1985). CMV was isolated on cell culture from blood, urine, and a throat swab. BW B759U

(Burroughs Wellcome) 7.5 mg/kg/day was administered for 21 days, with stabilisation and partial resolution of the retinitis (Figs. 4A, B, 18 December 1985). The right visual acuity improved to 6/18 and the left remained counting fingers. The peripheral neutrophil count was preserved at $2.3 \times 10^9/\text{litre}$.

Four weeks later, in January 1986, fresh retinal

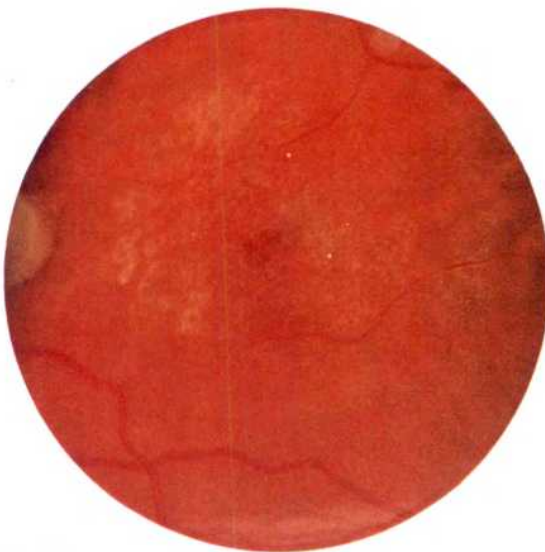


Fig. 4A

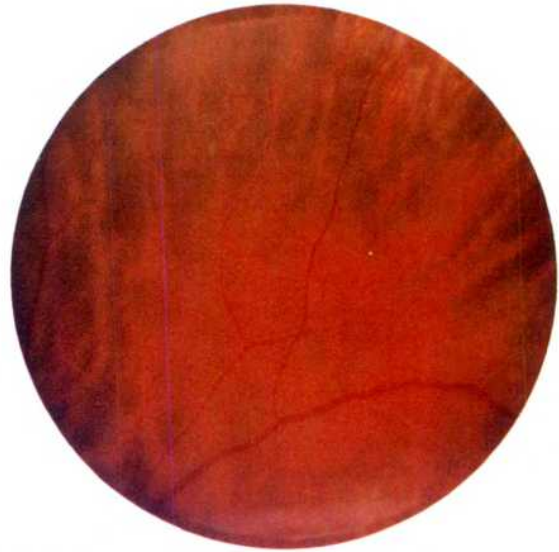


Fig. 4B

Figs. 4A, B *Resolution of the retinitis following a second course of DHPG.*

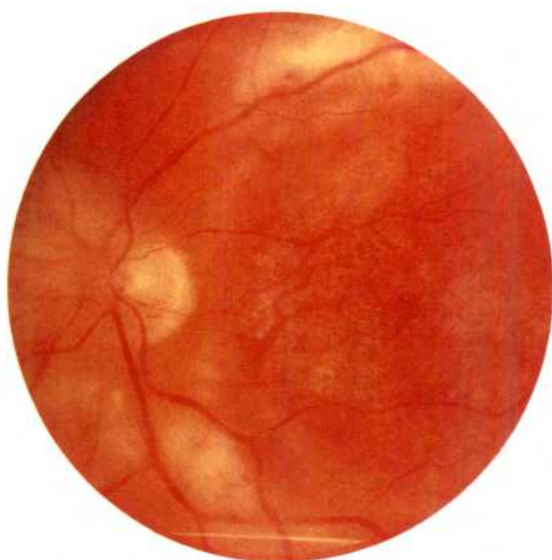


Fig. 5A

Fig. 5B

Figs. 5A, B Relapse and further retinal destruction four weeks later.

lesions were observed (Figs. 5A, B, 13 January 1986), and CMV was again isolated from urine. In view of the previous relapses after treatment with DHPG, Foscarnet (1.5 g loading dose followed by 0.15 mg/kg/min) was given intravenously for 19 days with only a marginal clinical response (Figs. 6A, B, 6 February 1986). The patient developed marked

superficial thrombophlebitis at the infusion sites, which made peripheral venous access increasingly difficult. No other adverse responses to this treatment were observed.

BW B759U 7.5 mg/kg/day was then given for 14 days, with marked improvement (Figs. 7A, B, 5 March 1986), and this time the patient was dis-

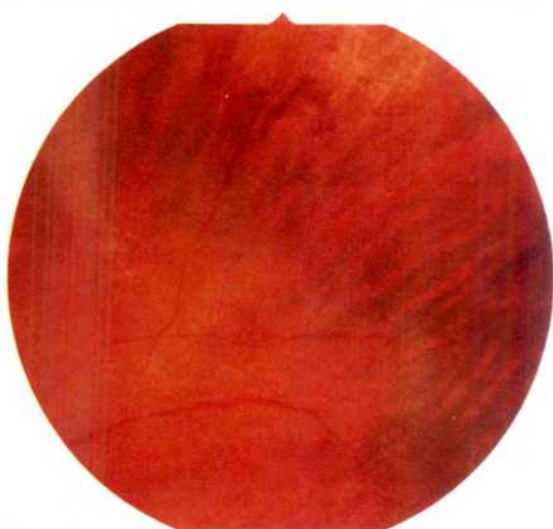
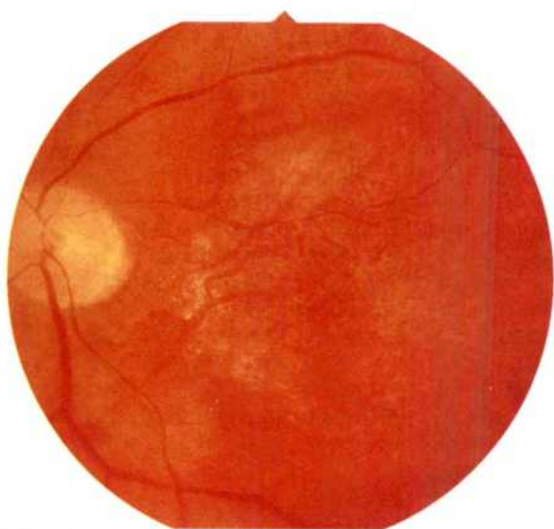


Fig. 6A

Fig. 6B

Figs. 6A, B After 19 days' treatment with Foscarnet there was partial improvement in the retinopathy, but retinal infiltration remained here and in other areas of both eyes. The drug produced marked superficial thrombophlebitis at intravenous cannula sites.

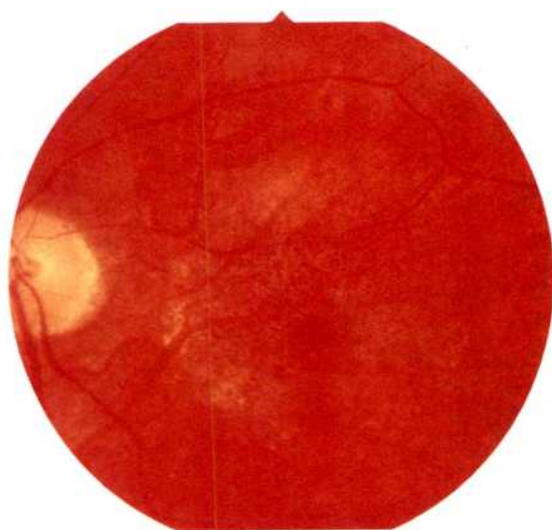


Fig. 7A

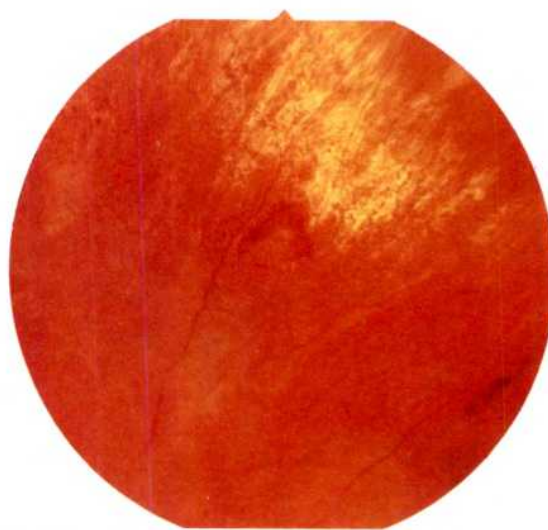


Fig. 7B

Figs. 7A, B A third course of DHPG cleared the retinitis, leaving areas of marked retinal atrophy.

charged on a maintenance regimen of 5 mg/kg three times weekly. The retinal lesions remained stable for six weeks, when the patient was readmitted because of fresh retinitis, weight loss, malaise, and salmonellosis. DHPG 7.5 mg/kg/day was given for 21 days. The patient died on 12 May. The course of the retinitis and treatment periods are summarised in Fig. 8.

At necropsy, the cause of death was found to be bronchopneumonia. Histology supported the clinical diagnosis of CMV retinitis, but viral cultures were negative.

Discussion

9-(1,3-Dihydroxy-2-propoxymethyl) guanine (DHPG, also known as BW B759U) is an acrylic purine analogue with antiviral activity against all herpes viruses, with a 30-fold greater activity against cytomegalovirus than acyclovir. The triphosphate metabolite of DHPG competitively inhibits viral DNA polymerase in a similar manner to acyclovir, affording relatively selective activity against cytomegalovirus infected cells. The principal adverse reactions are due to dose-related cytotoxicity causing neutropenia, inhibition of spermatogenesis, and gastrointestinal mucosal atrophy and necrosis. DHPG is administered by intravenous infusion over one hour, and a therapeutic effect is achieved in doses of 2.5 mg to 15 mg/kg/day given in two or three divided doses.^{10,11} Shepp *et al.*¹² have shown that neutropenia developed when mean peak and trough plasma levels exceeded 50 and 10 $\mu\text{mol/l}$ respectively,

and that these levels were found in three out of five patients receiving 15 mg/kg/day and in none receiving 7.5 mg/kg/day. However, others¹³ have reported neutropenia in two out of six patients at doses of 7.5 mg/kg/day. Penetration of the central nervous system is high, with levels 38% of simultaneous blood levels, and 91% of the daily dose is excreted unchanged in the urine.¹²

Trisodium phosphoformate hexahydrate (Foscarnet) is an agent with activity against reverse transcriptase from a large number of retroviruses and DNA polymerases from herpes simplex types 1 and 2 and CMV. At plasma concentrations of 32–55 $\mu\text{mol/l}$ cellular DNA polymerase is inhibited. Cell cultures of herpes viruses and the animal retrovirus visna (which is related to HIV) are inhibited by 100 $\mu\text{mol/l}$ of Foscarnet. In-vitro inhibition of HIV has also been described.^{14,15} Cellular toxicity is low, and the drug is eliminated rapidly in the urine. Foscarnet is given continuously as a 2% solution by intravenous infusion because of its short half-life, and only small amounts enter the central nervous system.^{14,15} A loading dose of 10–20 mg/kg followed by a continuous infusion of 0.5–0.15 mg/kg/min is calculated to achieve a steady state plasma level of 50–150 $\mu\text{g/l}$. Adjustments are made according to renal function.¹⁶

Clinical cases of resolution of CMV pneumonitis and retinitis in AIDS patients after the administration of DHPG have recently been reported from North America.^{12,13,17–20} This year the Collaborative DHPG Study Group has reported resolution of disease activity and clearance of viraemia in nine out

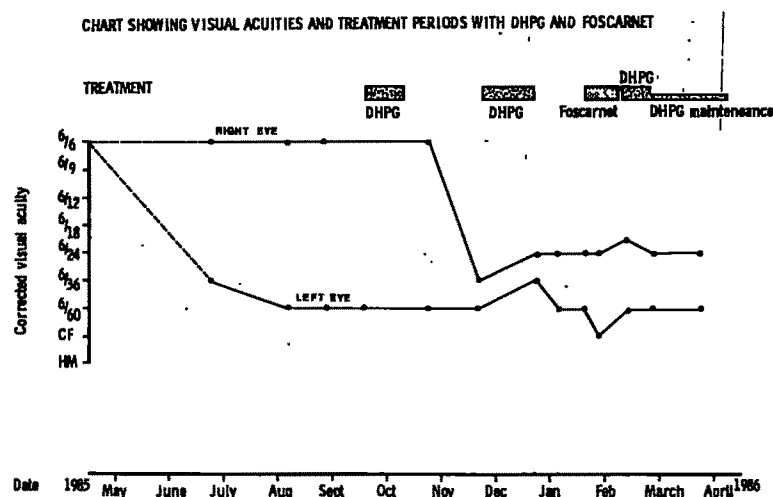


Fig. 8 Flow chart of the patient's treatment and visual acuity.

of 11 patients with CMV retinitis.¹⁹ Palestine *et al.*²⁰ reported the results of treatment with DHPG of 14 eyes in eight patients with CMV retinitis, eight of which demonstrated more than 90% resolution and four a partial response. Two out of these patients had chemotherapy induced immunosuppression and achieved remission for two and six months respectively. The remaining six patients had AIDS. Three were followed up and relapsed within 32 days of stopping treatment. One went on to further treatment, followed by maintenance therapy in reduced doses because of neutropenia and died four months after presentation. Rosencan *et al.*¹³ reported a response in all of a group of six patients with AIDS. Three relapsed within 21–28 days of cessation of treatment and three were lost to follow-up. Further treatment of one patient again was limited by drug induced neutropenia. These studies indicate that an initial response to DHPG is often obtained but that early clinical and virological relapse is common and that reversible neutropenia is the principal adverse reaction.

Reports of the clinical efficacy of Foscarnet in the treatment of disseminated CMV infection in the immunodeficient have appeared recently.^{21,22} However, there is only one report of the treatment of CMV retinitis in AIDS. Singer *et al.*²³ describe satisfactory resolution in one patient who also received adjunctive cytomegalovirus hyperimmune globulin and emphasise the relatively long remission of five months which was obtained.

We report a more satisfactory response to DHPG than to Foscarnet without using hyperimmune globulin. This apparent superiority may relate to limited penetration of the blood-brain barrier by Foscarnet.¹⁹ Our experience was similar to others¹ in that, although the retinitis responded initially to

treatment, relapse invariably occurred 4–8 weeks later.^{13,18–20} Maintenance therapy with three times weekly DHPG did not affect the relapse time in our patient. Although Bach *et al.*¹⁸ reported a remission of over eight weeks in one patient, the role of maintenance treatment, its frequency, and the dosage require further clarification, especially in view of the practical problems associated with intravenous therapy in AIDS patients.

We are grateful to Syntex Research for supplying the DHPG, to Burroughs Wellcome for the BW B759U, and to Astra Pharmaceuticals for the Foscarnet.

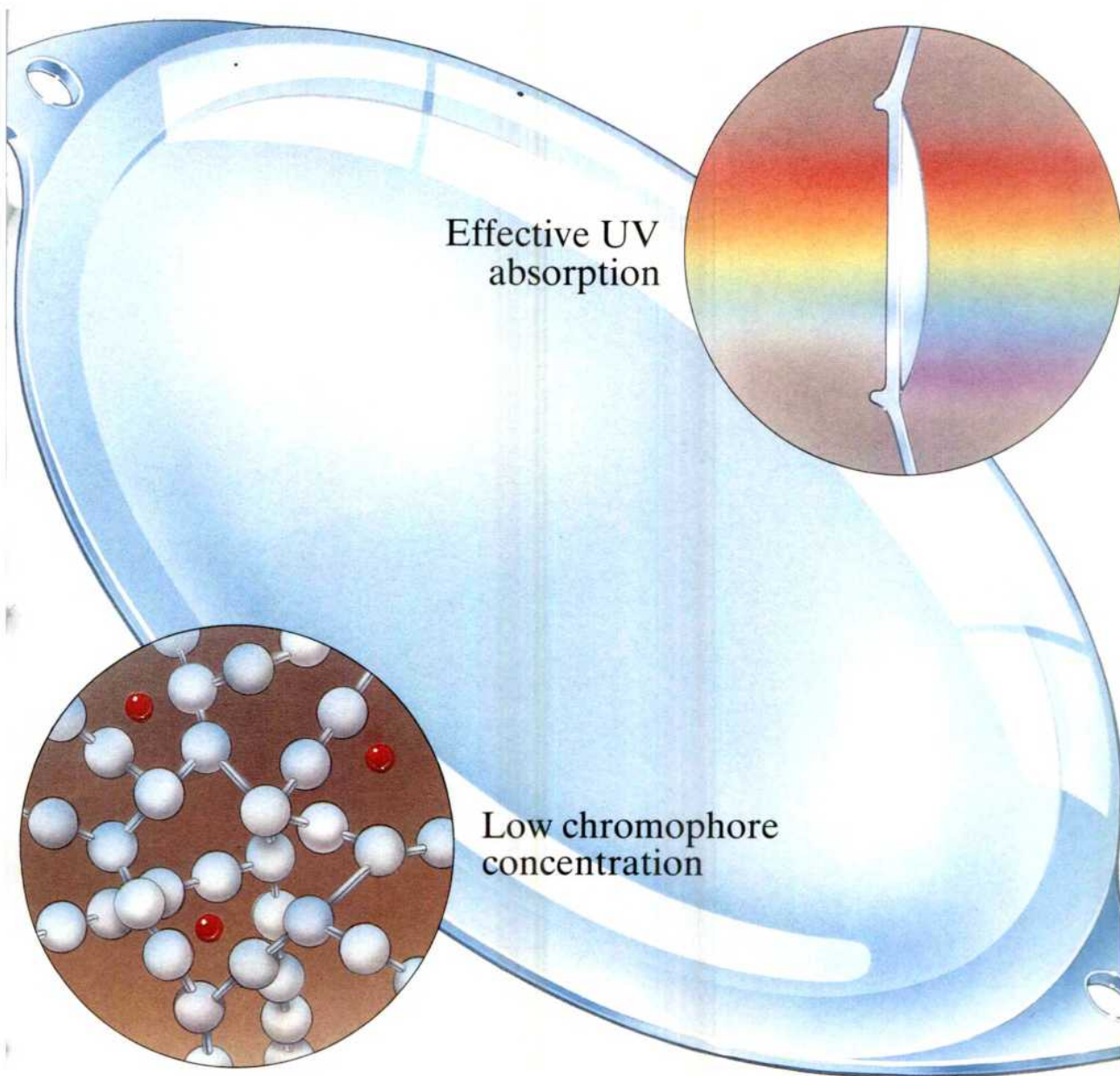
The fundus photographs were taken by Mr Richard Dewhurst, and Astra Pharmaceuticals kindly made a donation towards the costs of photographic reproduction.

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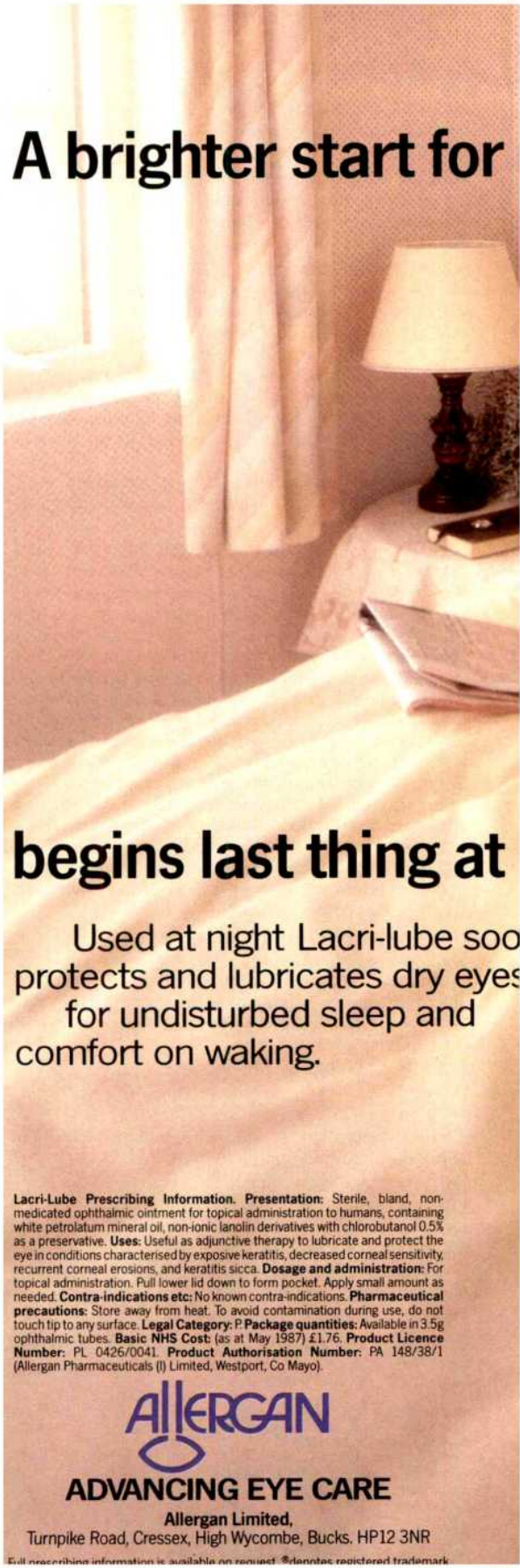
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Retinal arterial macroaneurysms: a retrospective study of 40 patients

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SUMMARY We studied 40 patients with a total of 44 retinal arterial macroaneurysms. All patients were followed up for at least six months. Macroaneurysms (MAs) have variable clinical presentations and are still frequently misdiagnosed before fluorescein angiography. Haemorrhagic MAs were most frequently misdiagnosed (75%), and had a sudden onset with a relatively poor visual outcome. Patients with these MAs had higher systolic blood pressures and significantly fewer associated retinal vein occlusions ($p<0.05$) than other types of MA. Exudative MAs caused a gradual onset of symptoms, were frequently associated with retinal vein occlusions, and were the most frequent indication for laser treatment. Only one of 10 quiescent MAs subsequently developed significant exudation or haemorrhage. We confirm the association of MAs with retinal and systemic vascular disease. In addition we found that MA patients had a significantly higher blood packed cell volume (haematocrit) than controls ($p<0.05$). Laser treatment significantly shortened the duration of MA patency ($p=0.006$).

Retinal arterial macroaneurysms (MAs) are acquired aneurysmal dilatations of the retinal arteries which usually occur in elderly, hypertensive people. The term macroaneurysm was introduced in 1973 to distinguish aneurysms of the retinal arteries from those of capillaries and veins.¹⁻³ Although Robertson's report was the first review, isolated cases of retinal arterial aneurysms have been described since the nineteenth century⁴⁻⁷ and a number in the past decade.⁸⁻²⁷ MAs appear as local arterial dilatations with variable degrees of artery wall hyalinisation and surrounding retinal exudate or haemorrhage. They are frequently associated with retinal vascular occlusions,^{1 10 13 23} retinal emboli,^{1 13} systemic hypertension,¹⁶ and vascular disease.¹⁰ Histological examination confirms the presence of a true aneurysm with vessel wall thickening, hyaline change, and elastotic degeneration.^{19 26}

Most reports have not classified MAs, although Palestine and colleagues' study²³ grouped MAs according to their position in relation to the vascular arcades and whether visual acuity was affected.

Nevertheless, visual loss is influenced not only by the proximity of the MA to the macula, but also by the presence of oedema, exudate, or haemorrhage and its severity, duration, and position. Since the MAs with visual loss and haemorrhage may have a different course and outcome than those with exudate,^{10 21} a classification reflecting this may be useful.

Spalter²⁴ has emphasised that MAs are often incorrectly diagnosed and regards them as a masquerade syndrome. The differential diagnosis includes Coats' disease, Leber's miliary aneurysms, von Hippel-Lindau syndrome, and very rarely venous macroaneurysms. It is important to differentiate MAs from retinal capillary aneurysms which may at times be large but do not arise from an artery and may therefore be treated without risk of vascular injury.

Photocoagulation of MAs was first described by Hudomel and Imre⁸ and has since been reported by several authors.^{16 21 23-25 27} Although visual acuity is often reported as improved after laser photocoagulation of the MAs with macular oedema or exudate, it may improve spontaneously. MAs are described as being obliterated within one to seven months of

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treatment, though no study has compared this with a large group of untreated cases.

Despite the fact that MAs are not rare, they are frequently misdiagnosed, the natural history is not clear, and only two reports have included more than 20 patients. Further information is required to define prognostic features and indications for and results of treatment. We were therefore prompted to review our series.

Material and methods

We retrospectively reviewed cases of angiographically proved retinal arterial macroaneurysms seen at the Western Ophthalmic Hospital, London, from 1973 to 1984. The cases were identified from a fluorescein punch card index. The patients' notes were studied, and where necessary patients were recalled for re-examination. Colour stereo photographs and fluorescein angiograms were examined and classified separately by two of the authors (MJL and RJM). Particular attention was paid to MA characteristics and positions, retinal vascular abnormalities, and to the presence of associated ocular disease. A thorough medical assessment was performed on 18 patients (45%) in the medical clinic supervised by Sir Stanley Peart. Particular attention was paid to the cardiovascular examination, and most patients had electrocardiography, chest x-ray, full blood count, and tests of electrolytes and urea performed. The blood packed cell volume and systolic blood pressure at or within six weeks of presentation were available in a number of patients and were compared between groups and with age matched controls. All cases had a minimum of six months' follow-up.

Clinically and histologically MAs are characterised by a dynamic process of formation, enlargement with or without blood-retinal barrier disruption, and gradual spontaneous resolution after a variable time period. Since the extent of blood-retinal barrier disruption determines the nature of visual impairment, we classified MAs in terms of their barrier function:

Quiescent MAs, with haemorrhage or exudate extending for less than 1 disc diameter and sparing the macula (Fig. 1).

Exudative MAs, in which exudate is the major component measuring more than 1 disc diameter and is responsible for visual loss in cases combined with haemorrhage (Fig. 2).

Haemorrhagic MAs with haemorrhage extending more than 1 disc diameter, more extensive than any associated exudate, and responsible for visual loss (Fig. 3).

Argon laser photocoagulation was performed on 10 patients, five with exudative MAs and five with

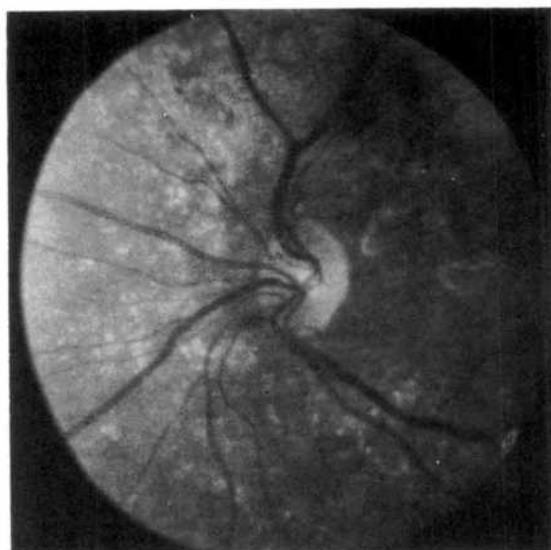


Fig. 1 Fundus photograph of a quiescent macroaneurysm, with minor local intraretinal haemorrhage.

haemorrhagic MAs. In the haemorrhagic group two MAs were treated because of the development of macular oedema or exudate, while three were treated to prevent further haemorrhage. The technique consisted of applying a ring of argon laser photocoagulation (Coherent 200 source) two or three burns in width to the retina immediately surrounding

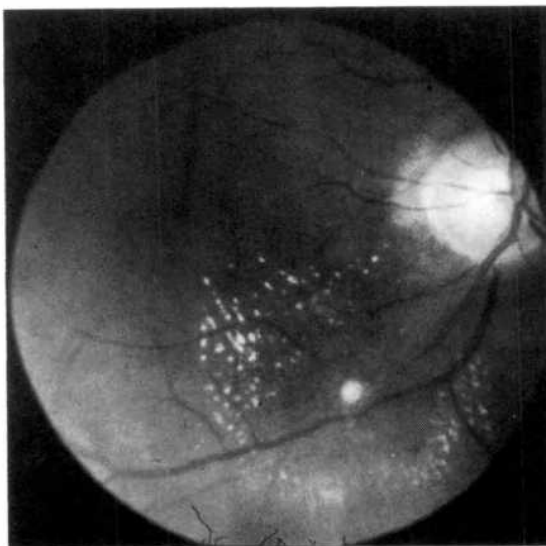


Fig. 2 Fundus photograph of an exudative macroaneurysm. Hyalinised, pale macroaneurysm is located at arterial bifurcation and surrounded by retinal oedema. Exudate is approaching the fovea.

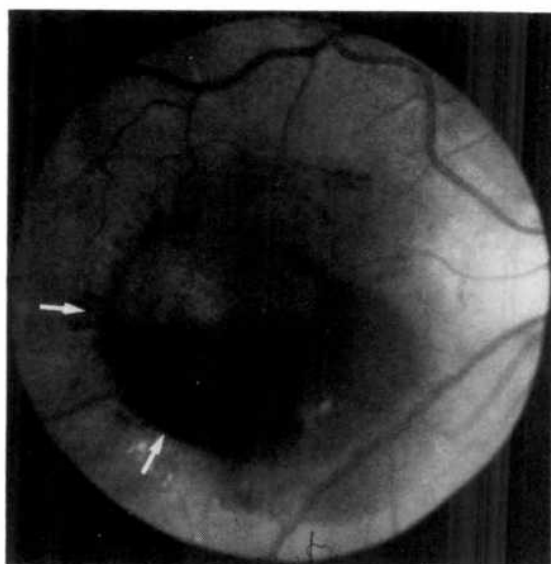


Fig. 3A

Fig. 3 Fundus photograph (A) shows haemorrhagic neuroretinal detachment (arrows) with adjacent subretinal haemorrhage. Venous phase of fluorescein angiogram (B) shows macroaneurysm partially masked by overlying haemorrhage, with proximal arterial constriction.

the MA sufficient to obtain mild to moderate retinal blanching. Burns were then placed on the aneurysm itself using similar intensity until the MA was blanched. Treatments employed a spot size of 100 to 200 μm with a duration of 0.1 to 0.2 seconds; nine MAs required an average of 52 burns, while two

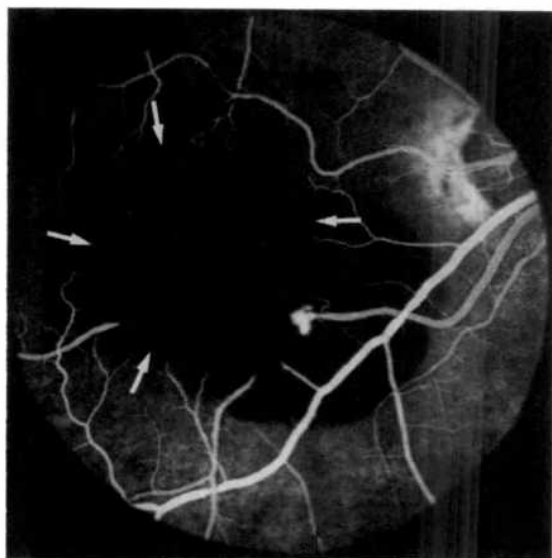


Fig. 3B

others needed over 300 burns each. The intensity and number of burns required depend on media clarity and local tissue swelling and uptake characteristics.

Results

A total of 44 MAs were identified in 43 eyes of 40 patients, and in 37 patients the MAs were single. Three patients had more than one MA, with bilateral involvement in all 3 (7.5%).

Sex. A definite female excess was noted, with 28 females (70%) and 12 males. The age specific incidence of MAs in the general population was greater for females (Fig. 4).

Age. The age at presentation ranged from 55 to 89 years, with a mean of 66.1 years. The incidence of MAs was found to rise with age (Fig. 4).

Clinical appearance and examination of stereo colour photographs disclosed a set of clinical signs in 86% of affected eyes which included a local retinal arterial dilatation surrounded by a ring of hyaline change and intraretinal haemorrhage with overlying retinal oedema. In some patients these signs were partly masked by overlying retinal haemorrhage, but in most an accurate diagnosis was possible from examination of the stereo colour photographs alone. Serous neuroretinal detachment was seen in four patients, with macular involvement in two. In most patients the classification as haemorrhagic or exudative was obvious. In seven patients with haemorrhagic MAs a minor degree of exudate was seen about the peripheral margins of retinal haemorrhage, and two of these later required laser treatment for macular oedema or exudate. Subretinal haemorrhage was present in 20 of the 21 eyes with haemorrhagic MAs. This gradually resorbed over a period of months, leaving a variable degree of pigment

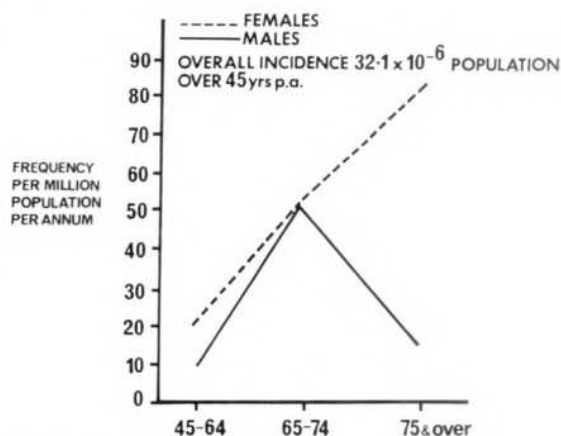


Fig. 4 Age specific incidence of macroaneurysms as calculated from catchment population.

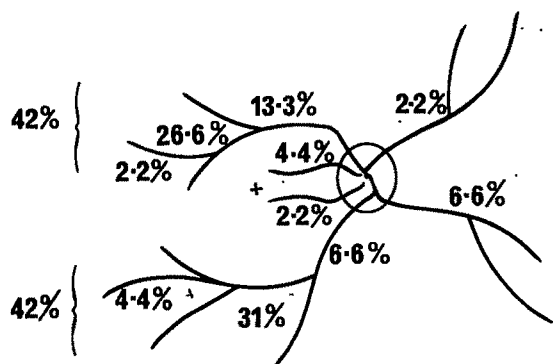


Fig. 5 Distribution of retinal arterial macroaneurysms.

epithelial disturbance and subretinal scarring in its wake. Haemorrhagic MAs resolved spontaneously in all but two patients, both of whom suffered recurrent bleeds. One of these had received laser photocoagulation to the MA some weeks before recurrent haemorrhage.

Site. The right eye was affected in 17 patients and the left in 20. The remaining three patients had bilateral involvement. MAs were as frequent on the superotemporal vessels as on the inferotemporal vessels (Fig. 5). Most MAs (84%) were seen on the temporal vascular arcades. Haemorrhagic MAs were located significantly closer to the optic disc (40% within 1.5 disc diameters) as compared with other MAs (16%, $p < 0.05$). MAs were commonly found in association with arterial bifurcations or arteriovenous crossings.

Presentation. The commonest presenting feature was acute loss of vision, either central or generalised due to haemorrhage, and occurred in 21 eyes of 20 patients (52.5%). Visual loss was central as a result of macular haemorrhage in 15 eyes, and was generalised

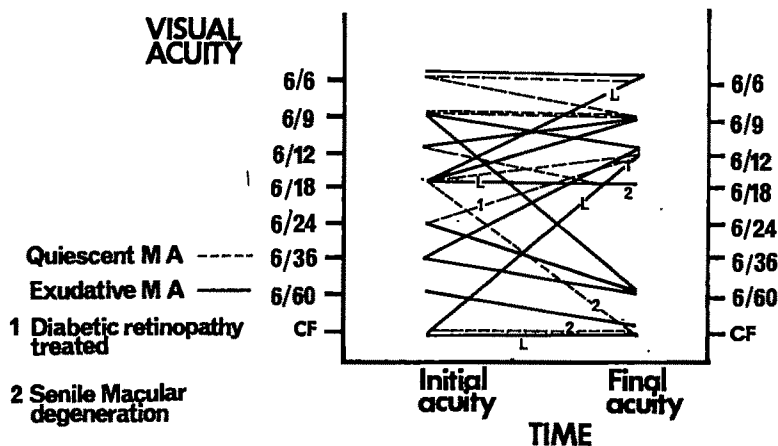
owing to vitreous haemorrhage in six. The mean duration of symptoms before presentation in haemorrhagic MAs was 1.4 weeks.

A total of 13 eyes of 13 patients (32.5%) were found to have exudative MAs. These patients had a significantly longer duration of symptoms before presentation (mean 16.6 weeks, $p < 0.05$), with gradual and often progressive central visual impairment. No patient in this group experienced late haemorrhage or recurrent exudation after apparent resolution of the MA. Four patients had a minor degree of associated intraretinal haemorrhage. A further patient had a significant degree of subretinal haemorrhage, though macular exudate was the major feature.

A total of 11 quiescent MAs were identified in 10 eyes of eight patients. One eye included two quiescent MAs. One patient had a quiescent MA which subsequently ruptured, and this patient is included in the haemorrhagic group for analysis. No other quiescent MAs developed exudation or haemorrhage. Quiescent MAs were discovered incidentally in three patients who presented with retinal vein occlusions, two with macular degeneration, one with diabetic retinopathy, a fellow eye to a haemorrhagic MA, and one patient with lens opacities.

Visual outcome. Initial and final visual acuities are summarised in Figs. 6 and 7. Initial visual acuities of counting fingers or worse were common in haemorrhagic MAs (52%) but unusual in exudative MAs (15%). In general the outcome was relatively benign, with 54% of exudative MAs and 48% of haemorrhagic MAs retaining an acuity of 6/12 or better. Poor visual outcome (counting fingers or worse) was seen in 24% of haemorrhagic MAs and 15% of exudative MAs and was related to the severity and duration of macular involvement. Two eyes with exudative MAs

Fig. 6 Initial and final visual acuities in eyes with quiescent (dashed lines) and exudative (continuous lines) macroaneurysms: 22 eyes.



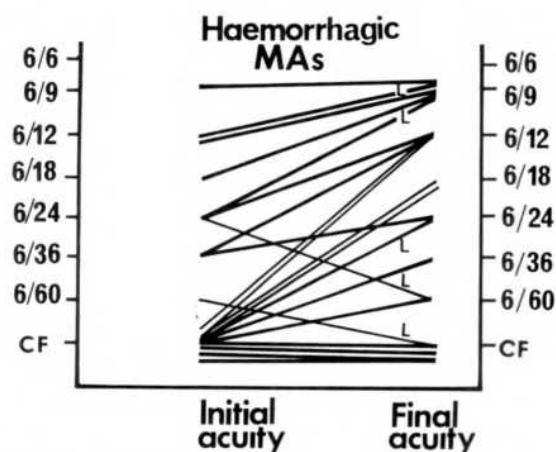


Fig. 7 Initial and final visual acuities in eyes with haemorrhagic macroaneurysms: 21 eyes. L=laser treated eye.

suffered a reduction in visual acuity of two or more lines owing to macular exudation; in both cases laser treatment had been recommended but was refused. Only two eyes with quiescent MAs suffered reduced acuity, due to senile macular degeneration in both (Fig. 6). The causes of poor final visual acuity are summarised in Table 1. When laser treated groups were compared with untreated groups for different types of MA, no difference in visual outcome was found.

Duration. Follow-up visits for all MAs ranged from a minimum of six months to seven and a half years, with a mean of two years and five months. The duration of MA patency from diagnosis to resolution could be established in seven treated and 14 untreated cases. The total duration of MA patency was significantly shorter in laser treated cases (mean 3.5 months) as compared with untreated cases (mean 13.6 months, $p=0.006$, Fisher's exact test), MAs in six out of seven treated eyes resolved within one month of laser treatment, as proved on post-treatment angiography. The duration of untreated MAs ranged from three months to seven years. Haemorrhagic MAs resolved spontaneously in all but two patients, both of whom suffered recurrent haemorrhage (5%). One of this pair had received laser photocoagulation to the MA.

Fluorescein findings. Angiography showed that MA sizes were variable, with larger MAs on the

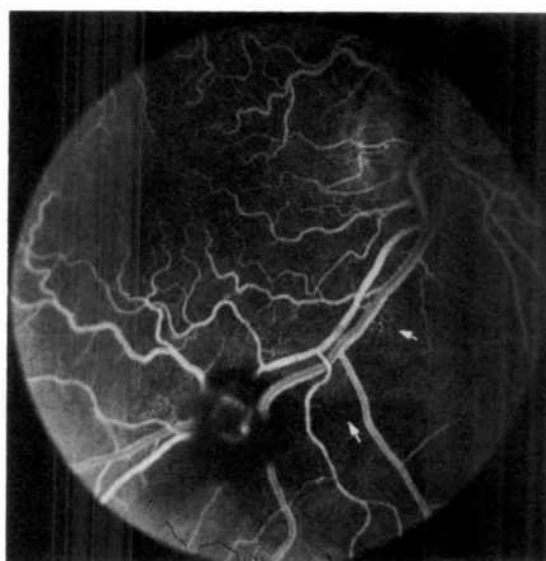


Fig. 8 Fluorescein angiogram in a patient with vitreous haemorrhage from a macroaneurysm discloses multiple areas of capillary telangiectasia and coarsening of the capillary network (arrows).

larger arteries. Aneurysms appeared to be fusiform or saccular. Fusiform MAs showed rapid filling in the early arterial phase and involved most of the arterial circumference. Saccular MAs showed minimal early filling, with good filling in the middle or late phases of the angiogram. The rate of filling seemed to be determined by the size of the aneurysm neck. Fluorescence of MAs was not necessarily homogeneous and many showed irregular inhomogeneous filling, thought to represent intraluminal clot formation. Occasionally the MA was masked by overlying blood, but subsequent angiograms demonstrated the MA. Focal areas of capillary dilatation, telangiectasia, or closure were seen in 48% of eyes. Although fine capillary changes were frequently seen in the retina adjacent to the MA, in many patients these capillary abnormalities were also located well away from the MA (Fig. 8).

Previous fundus photographs were available from 10 patients, six of whom had had previous angiography for a variety of conditions, most frequently retinal vein occlusion. Careful examination of these angiograms failed to disclose any reliable indicator of future aneurysm formation.

Associated ocular disease. Retinal vein occlusions were seen in the same or fellow eye of 13 patients (32.5%), one of whom had a central retinal vein occlusion. A further patient had a branch artery occlusion. Other associated ocular diseases included drusen (19 patients), lens opacities (nine), and epiretinal membranes (two). Retinal arterial plaques

Table 1 Causes of poor final visual acuity (counting fingers or less)

Macular haemorrhage with pigment epithelial scars	4 eyes
Macular exudate	2 eyes
Persistent vitreous haemorrhage	1 eye
Senile macular degeneration	2 eyes

were seen in the same or fellow eye of eight patients (20%), while irregular arterial calibres were noted in 16 patients (40%). Patients with haemorrhagic MAs had significantly fewer associated retinal vein occlusion (15%) as compared to non-haemorrhagic MAs (50%, $p < 0.05$). Half the vein occlusions were in the same eye as affected by the MA. In three branch vein occlusions the MA was situated at the point of vein occlusion, suggesting a causal role in the genesis of the occlusion. Two other MAs were found in the area of retina involved by vein occlusions.

Systemic disease (Fig. 4). Of the 18 patients examined in the medical clinic 17 were found to have evidence of systemic vascular or relevant metabolic disease. A survey of the patients general practitioners found that, of the remaining 22 patients, only four had no known vascular disease. Systolic blood pressures of 200 mmHg or more were more frequent in patients with haemorrhagic MAs (40%) than with other MAs (20%), but the difference was not significant. Blood packed cell volume (haematocrit) levels were available in 20 of our patients and were compared with those in a group of 40 cataract patients matched for age and sex. Haematocrits over 45% were significantly more frequent in MA patients (55%) than controls (20%, $p < 0.05$). A history of smoking was available in 15; four were non-smokers and two others had not smoked within the past five years. Two patients died during the study period, both of complications of vascular disease, yielding a mortality of 4.8%. One of these patients died before six months of follow-up and is therefore not included for further analysis.

Discussion

We found that MAs are still often misdiagnosed despite a number of reports describing their clinical features.^{13-21 23 24 27} We emphasise that in most MAs the dominant feature is haemorrhage into the retinal or vitreous spaces and, less commonly, retinal oedema or exudate. These changes may be widespread and often partly obscure the underlying MA, which is therefore easily overlooked. Thus haemorrhagic MAs often masquerade as disciform macular lesions, and MAs with exudation may be misdiagnosed as branch vein occlusions or diabetic retinopathy. Further diagnostic difficulties may arise because branch vein occlusion, senile macular degeneration, or diabetic retinopathy may be seen in these patients and the presentation ascribed to these conditions. It is most important to differentiate these entities because of the very different treatments available. The diagnosis of MA should be considered in all elderly patients with intraocular haemorrhage, retinal oedema, or exudate, particularly if atypical

features are present. Subretinal haemorrhage in MAs is typically extensive, dense, overlies an artery, is not centred on the macula, and has vitreous extension. Careful fundus examination supplemented by fluorescein angiography, which may have to be repeated several times, usually establishes the diagnosis.

The age range and sex ratios seen in the study are almost identical to those found on pooling those recorded in the world literature.¹⁴⁻²⁷ The predominance of females in this study is not due only to the excess of females in the older population (see Fig. 1). Cerebral aneurysms are most frequent in women after the age of 40, and it is likely that similar pathogenetic factors operate in these two types of aneurysm.

Palestine and colleagues' classification²³ of MAs did not differentiate between different types of macular involvement. Our classification was simple and identified groups of patients who differed in terms of visual outcome and associated diseases. Although several MAs had mixed haemorrhagic and exudative features, it was usually not difficult to determine the major feature. Subretinal macular haemorrhage is not remediable by laser treatment and usually results in severe visual loss. Macular oedema or exudate on the other hand is eminently treatable, particularly if seen early. Clearly quiescent MAs had the best outcome.

Isolated MAs are almost always seen in the elderly. Aging is associated with replacement of the smooth muscle of the arterial media by collagen and an increase in intimal collagen. The arteries lose their elastic recoil and become rigid and relatively dilated. These changes are similar to those seen in the sclerotic phase of hypertensive retinopathy, and Garner and Klintworth²⁸ noted that many age related changes may be the result of haemodynamic stress.

Haemorrhagic MAs were located significantly closer to the optic disc than other MAs. Arteries close to the disc have larger diameters and increased flow rates than peripheral vessels. These factors will increase transmural stress in these arteries, and may contribute to haemorrhage.

MAs frequently occur at arteriovenous crossings. At the point where arterial and venous walls are in contact the adventitial layer is absent, and the two vessels share a common coat.²⁹ The arterial wall has less structural support at this point and may be prone to aneurysm formation. Any associated venous disease may cause local arterial wall damage, contributing to MA formation.

Retinal vein occlusions are frequently seen in association with MAs, and are also described in other arterial diseases such as Coats' disease³⁰ and Leber's miliary aneurysms.³¹ They were uncommon in

association with haemorrhagic MAs but commonly seen in association with non-haemorrhagic MAs. This suggests that different factors are important in MA rupture, and mechanical factors may be significant. Perhaps these associations reflect the differing effects of widespread retinal vascular disease on high pressure vessels (arterial aneurysm formation) as compared with low pressure vessels (resulting in vein occlusion).

Hypertension is a prominent feature in MA patients.¹⁰ Hypertensive retinopathy is associated with poor retinal vascular autoregulation, plasma transudation, and subsequent vessel hyalinisation. A rigid, dilated arteriole with abnormal wall results.^{32,33} The higher systolic blood pressures seen in patients with haemorrhagic MAs may have contributed to haemorrhage both by the increased transmural tension and by a greater amplitude of pulsations, causing mechanical vascular damage. We could not determine the patients' activities at the time of rupture in a large enough sample. However, studies of cerebral aneurysms have shown that up to 50% ruptured during events associated with transient arterial hypertension, emphasising the importance of mechanical events,^{34,35} and studies of experimental aneurysms have emphasised the roles of both hypertension and increased haemodynamic stress.³⁶ In this respect macroaneurysms have been compared to Charcot's cerebral aneurysms, which may be implicated in the genesis of cerebrovascular accidents.³⁷

A compromised vessel wall of any aetiology may be less able to withstand further insults such as embolic damage, particularly in the presence of a high intraluminal pressure. Although MA formation is often ascribed to the mechanical effects of hypertension,^{10,14} several authors have drawn attention to the role of local vascular damage.^{13,18-20} Retinal arterial emboli are frequently seen in eyes with MAs, which have been shown to develop at sites of previous embolic occlusion.²⁰ Indeed, a detailed study of retinal emboli reported one patient with an arterial exudative lesion 'of unknown significance', and the published photograph was very suggestive of an MA.³⁸ We note that the distribution of MAs parallels that described for retinal emboli,³⁸ showing a marked preference for the temporal retinal vessels and posterior pole. Histologically, MAs are found in areas of arterial disease,¹⁹ and one eye had evidence of focal small vascular occlusions.¹⁹ The frequent finding in our study of focal capillary abnormalities in areas adjacent to and away from MAs may be a sequel of small platelet-fibrin emboli. These emboli can travel far down the arterial tree, breaking into small fragments which occlude vessels and subsequently resorb, leaving focal zones of capillary closure. Vascular remodelling can occur after

embolic occlusions,³⁹ and this may explain the frequent finding of focal capillary dilatation. These capillaries may leak and cause visual loss if located in the perifoveal area,¹⁰ though this was not seen in our series.

Systemic vascular disease other than hypertension was a prominent feature of our MA patients as it was in other studies. In some patients the MA was the first manifestation of underlying systemic vascular disease. In a few patients systemic vascular disease was not found at their initial visit, but appeared at later follow-up. We are not aware of haematocrit measurements in previous studies of MAs. Although raised haematocrits have been described in patients with retinal vein occlusions,⁴⁰ this did not account for the raised haematocrits seen in our MA patients. Although our sample was small, the raised haematocrits did not appear to be due to smoking. Raised haematocrits are commonly seen in systemic vascular disease.^{41,42} The raised haematocrits in our MA patients may reflect their underlying systemic vascular disease.

Although some authors have suggested that MA patients have a high death rate after diagnosis,^{1,13} this was not our experience. The 4.8% mortality observed over the study period is not alarming given the ages of our patients.

The management of MA patients requires a full investigation for systemic disease, with particular attention to hypertension and systemic vascular and embolic disease. MAs were seen almost exclusively in the sclerotic phase of hypertension, with evidence of long-standing retinal vascular changes. In the face of long-term retinal vascular damage control of hypertension is not likely to cause resolution of the MA, though it might reduce the risk of haemorrhage.

Ocular management depends on MA behaviour. Haemorrhagic MAs with intact maculae should be observed closely in the initial period, as occasionally patients develop macular exudate requiring treatment. In general these MAs resolve spontaneously and do not require treatment. It has been suggested that haemorrhagic MAs should be treated to prevent recurrent haemorrhage.²⁷ Both this and a previous study²³ have found that recurrent haemorrhage is extremely uncommon, and that there are no reliable indicators of impending haemorrhage. In particular, MA pulsation is not a reliable warning of impending haemorrhage.²³ On the basis of this evidence we believe that the major indication for treatment of haemorrhagic MAs is the development of macular oedema or exudate.

Our study shows that treatment results in a significantly shorter duration of MA patency as compared to untreated cases. Since visual loss from macular oedema or exudate depends on severity and dura-

tion, early photocoagulation of selected cases should be beneficial. When treated cases were compared with untreated cases, Palestine *et al.*²³ found no improvement in visual outcome after photocoagulation. Case selection is particularly important, as patients with long-standing exudate or oedema are unlikely to improve. This was certainly a factor in our patients and explains our finding that photocoagulation did not improve visual outcome. Complications of photocoagulation included occlusion of the distal arteriole and an increase in exudate accumulation soon after photocoagulation, necessitating great care in the treatment of lesions close to the macula.

Direct photocoagulation of the MA may contribute to occlusion of the distal arteriole and was seen in 27% of our 11 treated cases. However this event may occur spontaneously in the natural history of an MA, and indeed was found in 25% of Cleary's untreated cases.¹¹ Only a small number of our untreated cases underwent fluorescein angiography after resolution of their MA, and these cannot usefully be compared to our treated group. We found distal arteriolar narrowing in 19% of our untreated MAs on fluorescein angiography. Most MAs resolve spontaneously, and the process of vascular healing is inevitably accompanied by local vessel wall constriction, seen clearly on angiography. Distal occlusion may occur as a result, and presumably depends on the severity and extent of the repair response.

There are no histological studies of the mechanism of laser induced resolution of a MA. Clinical experience suggests that the argon blue-green laser results in thermal uptake both in the retinal pigment epithelium surrounding the MA (causing injury to the outer vessel wall) and in the haemoglobin and oxyhaemoglobin²⁴ in the arterial lumen (causing endothelial injury). The aim of perilesional retinal photocoagulation is to aid resolution of oedema, though there is evidence that photocoagulated retinal pigment epithelium may trigger proliferation of nearby retinal vascular endothelial cells.²⁴ This mechanism could also contribute to resolution of the MA. The immediate vasospasm and reduced flow are superseded by a vascular repair response which results in local vessel wall constriction and MA resolution.

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Neovascularisation associated with posterior uveitis

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SUMMARY Twenty-six patients (39 eyes) with retinal neovascularisation associated with ocular inflammation were identified from the retinal vasculitis clinic at St Thomas's Hospital. Eight patients had sarcoidosis, seven patients Behçet's disease, and 11 had idiopathic retinal vasculitis. Twenty-three patients had required systemic therapy to control the inflammation and 11 patients received laser photocoagulation. Fluorescein angiography showed significant capillary closure in 15 eyes and diffuse microvascular leakage in the remaining 24 eyes. All patients had posterior vitreous detachment. The visual prognosis was good despite vitreous haemorrhage being the presenting feature in 22 eyes, and the new vessels resolved in 70% of cases. However, laser treatment was followed by a significant increase in cystoid macular oedema ($p < 0.01$). This retrospective study suggests that medical therapy is the first line of treatment in this group of patients. Photocoagulation should be performed when the eye is quiet and should be reserved for patients with recurrent vitreous haemorrhages and significant capillary closure.

Neovascularisation affecting the retina and optic disc is an unusual but a well recognised complication of posterior uveitis.^{1,2} Such vessels may give rise to vitreous haemorrhage, which contributes significantly to the visual morbidity in this disease. The neovascularisation is associated in some cases with capillary closure on fluorescein angiography, and an angiogenic factor produced by ischaemic retina has been implicated in the pathogenesis.^{3,4} However, new vessels may also appear in the eye unassociated with capillary closure, and fluorescein angiography shows diffuse microvascular leakage. In these cases it has been postulated that the neovascularisation is a direct result of the inflammatory process, a causal relationship being inferred from the fact that the vessels tend to regress with adequate control of the inflammation.⁵ The natural history of this complication has not been adequately studied, and at present therapy is directed towards control of the inflammation with systemic immunosuppressants, with laser photocoagulation being reserved for direct treatment of neovascular fronds, or the ablation of ischaemic areas. We have examined the clinical course of neovascularisation in a retrospective study and the effects of medical and laser treatments.

Patients and methods

The records of 200 patients with posterior uveitis of non-infectious aetiology who attended the Ophthalmology Department at St Thomas's Hospital over the last 12 years were examined. All patients with diabetes mellitus, systemic vascular disease, or haematological disorders were excluded from the study. Twenty-six patients were identified with retinal neovascularisation due to inflammatory eye disease rather than primary retinal ischaemia. Fifteen patients were male and eleven female. Eleven patients had a diagnosis of idiopathic retinal vasculitis, eight had histologically confirmed sarcoidosis, and seven had Behçet's disease. The age of the patients ranged from 6 to 45 years (mean 27 years). Patients had been followed up for a period of six months to 12 years (mean 4 years).

At each hospital visit a full ophthalmological assessment had been carried out, with particular note being made of inflammatory activity within the eye, the size and location of sites of neovascularisation and any associated retinal features—for example, periphlebitis, venous occlusion. Fluorescein angiography had been performed in all cases when new vessels were first noted, and follow-up angiograms were performed whenever clinically indicated. Initially patients had been treated with a combination of topical and systemic steroids (daily dose of 60–80

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mg prednisolone daily, tapering as the ocular inflammation was controlled). In some cases other immunosuppressants (azathioprine, chlorambucil, colchicine, and cyclosporin A) had been added to this regimen, either to increase the anti-inflammatory effect or as steroid sparing agents. The indications for laser photocoagulation of peripheral retina in this series were recurrent vitreous haemorrhage, significant capillary closure on fluorescein angiography (at least one quadrant), or neovascularisation which was unaffected by full immunosuppressive treatment. The visual acuity was recorded at the end of follow-up and the reasons for a poor corrected visual acuity (worse than 6/9 Snellen) were documented. Some illustrative case histories are presented below.

Case reports

CASE 1

A 16-year-old schoolgirl presented with a two-year history of intermittent poor vision in her right eye. Her general health was good and general examination was unremarkable. Visual acuity was 6/9 in the right eye and 6/5 in the left, and she had moderate posterior uveitis with ++ vitreous cells and some snowballs in both eyes. Two months later her right vision suddenly dropped to counting fingers due to a vitreous haemorrhage which, cleared to reveal new vessels on the right disc (Fig. 1A). Fluorescein angiography showed peripheral microvascular leakage but no capillary closure (Fig. 1B). She was treated with systemic steroids, and despite a further

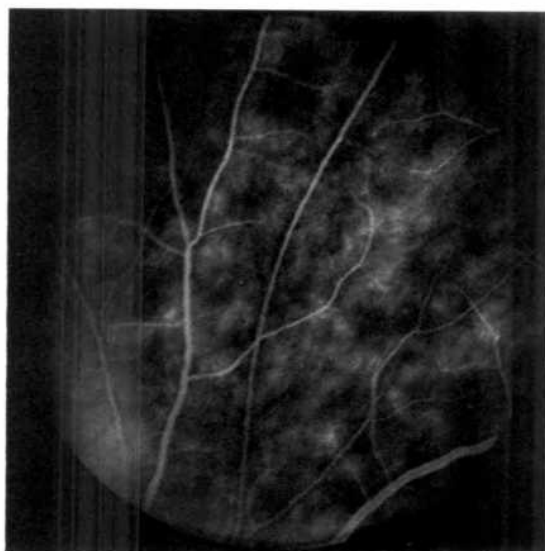


Fig. 1B Arteriovenous phase of fluorescein angiogram of the right eye. Diffuse capillary leakage of dye is present, but there is no capillary closure.

vitreous haemorrhage the new vessels disappeared three years after presentation (Fig. 1C) and her vision returned to 6/5 in each eye.

Comment. This case demonstrates that neovascularisation may regress with control of intraocular inflammation alone.

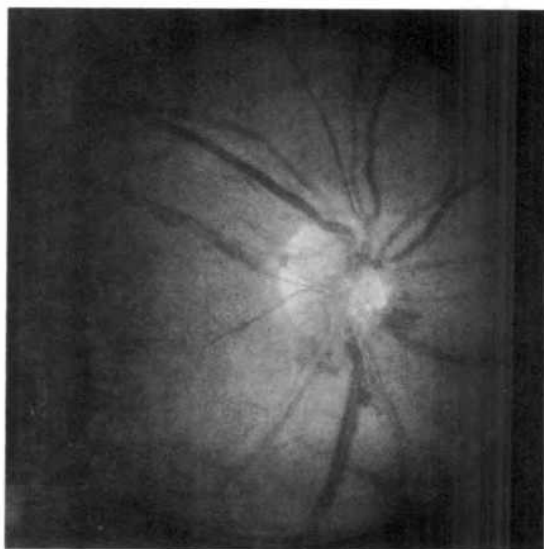


Fig. 1A Patient 1. Photograph of the right fundus showing extensive new vessels on the optic disc.

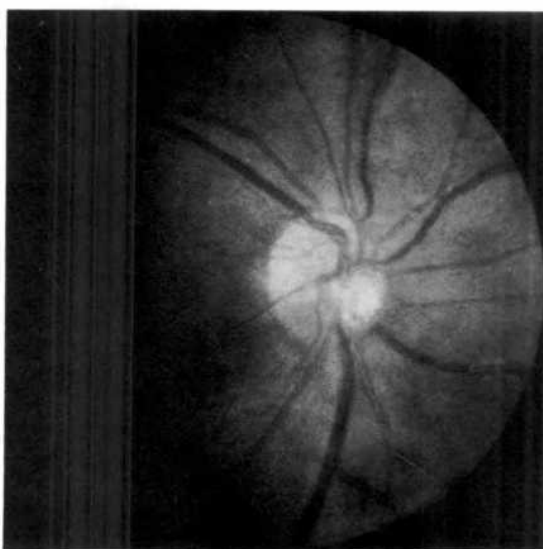


Fig. 1C Photograph of the right fundus three years after presentation confirms that the disc new vessels have resolved.

CASE 2

A 34-year-old bricklayer had been diagnosed as a case of Eales' disease 11 years previously. On presentation to St Thomas's in 1976 the visual acuity was counting fingers in the right eye and 6/9 in the left. He had bilateral vitreous haemorrhages. The right fundus could not be seen, but the left showed extensive peripheral retinal new vessels, and capillary closure was demonstrated on fluorescein angiography. He was initially treated with laser photocoagulation to the left eye, but despite this he developed new vessels at the optic disc (Fig. 2A). He was treated with systemic steroids and a further course of laser treatment, and both the disc and peripheral new vessels regressed. However, his visual acuity remained poor at counting fingers in both eyes due to chronic macular oedema (Fig. 2B).

Comment. This case illustrates that combined medical and laser treatment may be required to control neovascularisation but that cystoid macular oedema may develop despite such treatment.

CASE 3

A 28-year-old housewife had suffered from Behçet's disease for 10 years. On admission to St Thomas's Hospital the visual acuity was counting fingers in the right eye and 6/5 in the left. She had had recurrent vitreous haemorrhages in the right eye in which a traction retinal detachment involving the macula was present. An upper nasal branch vein occlusion was present in the left eye (Fig. 3A). New vessels were present on

both the optic discs (Fig. 3B, C). She was treated with a reducing dose of systemic steroids, beginning with 60 mg daily, and the new vessels on the left optic disc resolved. However, she recently suffered a left inferotemporal branch vein occlusion involving the macula and has consequently developed more disc new vessels in the left eye (Fig. 3D).

Comment. This case illustrates that new vessels may settle spontaneously on medical treatment despite the presence of capillary closure.

CASE 4

A 34-year-old soldier with histologically confirmed sarcoidosis initially presented with blurred vision in the right eye due to posterior uveitis. The inflammation resolved following a course of systemic steroids, but six weeks later vision in the right eye was reduced owing to a vitreous haemorrhage. Fundus examination showed optic disc and peripheral neovascularisation associated with capillary closure (Fig. 4A). Right panretinal photocoagulation was carried out, and the abnormal vessels regressed (Fig. 4B). Six years later he presented with a further vitreous haemorrhage in the right eye, and more peripheral new vessels had developed. Further laser treatment was unsuccessful, and the right vision remained at hand movements due to persistent vitreous haemorrhage.

Comment. This case illustrates the initial beneficial effect of laser photocoagulation in the presence of capillary closure, though further treatment failed to produce regression of the new vessels.

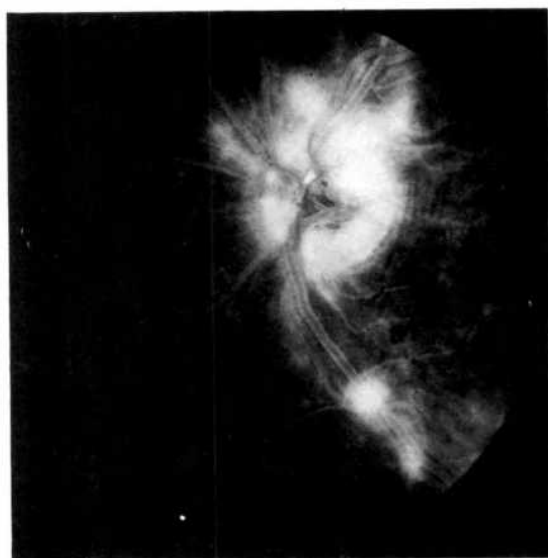


Fig. 2A Patient 2. Venous phase fluorescein angiogram of the left eye shows new vessels on the optic disc and along the inferotemporal artery.

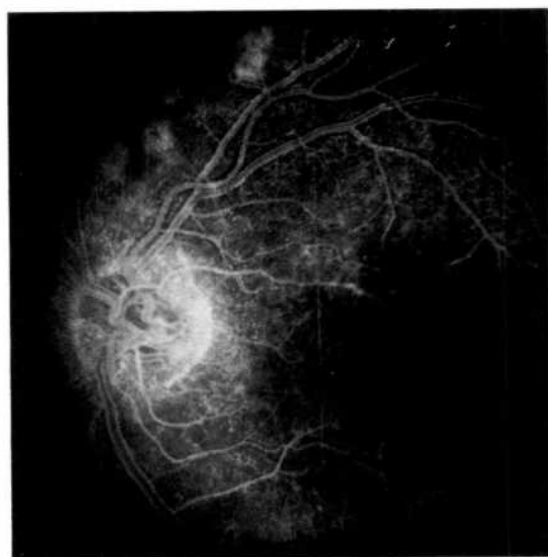


Fig. 2B After laser treatment the fluorescein angiogram confirms the presence of cystoid macular oedema in the left eye.



Fig. 3A Patient 3. Fluorescein angiogram of the right eye demonstrates capillary closure with collateral vessels in the upper nasal quadrant.

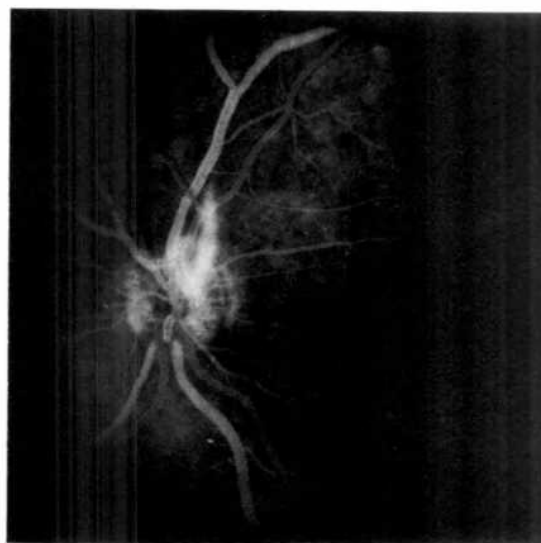


Fig. 3C The fluorescein angiogram of the left eye demonstrates new vessels in the superior margin of the optic disc.

Results

In this study of 26 patients with retinal neovascularisation due to posterior uveitis, 39 eyes showed evidence of new vessels. Vitreous haemorrhage was a presenting feature in 22 eyes (56%), and in 12 of these (31%) it was a cause of significant visual loss

(reduction of more than 3 lines on the Snellen chart). New vessels were found at the optic disc in 28 eyes (72%) and elsewhere in the retina in 11 (28%). Active inflammation in the posterior segment (2+ cells or more), and a posterior vitreous detachment was present in all affected eyes.

The fluorescein angiographic features are pre-

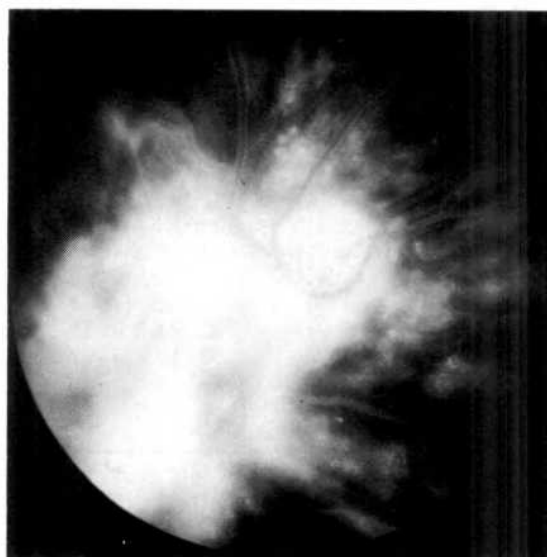


Fig. 3B Late phase fluorescein angiogram of the right eye. There is leakage of dye from the optic disc and the neovascular frond extending from the disc to the macula.

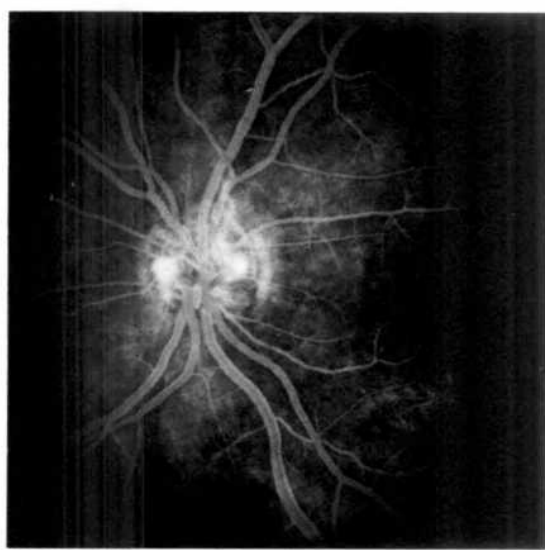


Fig. 3D Fifteen months later the fluorescein angiogram of the left eye reveals that the new vessels on the superior margin of the disc have regressed but new ones have developed in the medial and lateral portions of the disc.

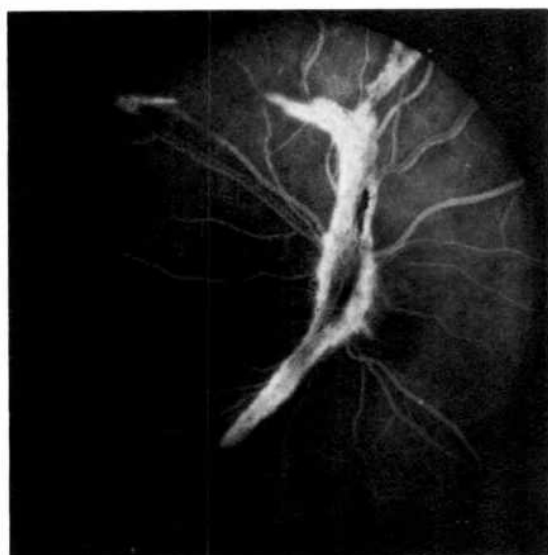


Fig. 4A Patient 4. Fluorescein angiogram of the right eye at presentation. A large neovascular frond extends from the optic disc.

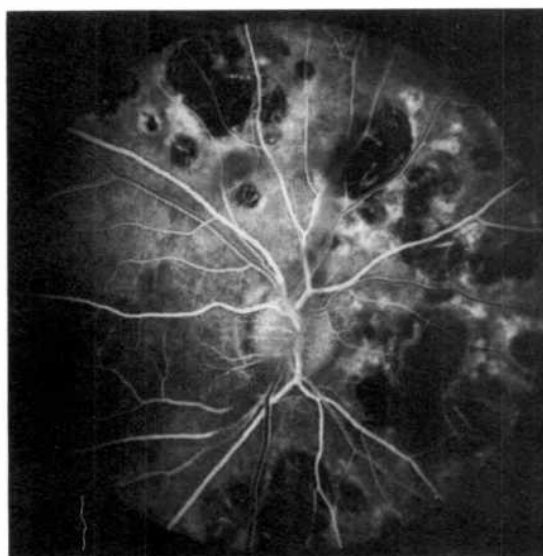


Fig. 4B The fluorescein angiogram was repeated six months after panretinal photocoagulation was performed and confirmed regression of the new vessels.

sented in Table 1. These features fell into two main groups at presentation. New vessels were present in association with significant capillary closure (at least one quadrant) in 15 eyes (38%), and in half of these a branch vein occlusion was present. In the remaining 24 eyes significant capillary closure was not found, but diffuse microvascular leakage was present, and frank venous leakage associated with periphlebitis was seen in 12 eyes—some eyes having both. Cystoid macular oedema appeared in 16 eyes, eight with capillary closure and eight without such changes.

The treatment that the patients received is summarised in Table 2. Topical steroids were given to all patients except one who received no treatment of any sort. Twenty-three patients received courses of systemic steroids and six patients required additional immunosuppressives. Eleven patients received laser photocoagulation (eight panretinal, three localised to areas of capillary closure), and in one patient this was the only treatment given. Direct photocoagulation to neovascular fronds was not given, and surgical intervention as a primary procedure for vitreous

haemorrhage was not performed in any patient. The change in visual acuity from initial presentation to most recent follow-up visit, with special reference to those eyes that had vitreous haemorrhages and laser photocoagulation, is shown in Figs. 5 and 6. The visual prognosis was generally good in the presence of vitreous haemorrhage, but some patients who received laser treatment showed subsequent deterioration mainly due to the development of cystoid macular oedema.

The complications which arose during treatment are documented in Table 3. Cystoid macular oedema developed significantly more often in eyes that received photocoagulation than in those that did not ($p < 0.01$; χ^2 test; Table 4). Traction retinal detachment was rare, possibly because all eyes showed posterior vitreous detachments. Persistent visual loss due to vitreous haemorrhage occurred only in two eyes, and a posterior subcapsular cataract in one eye.

The fate of the new vessels is shown in Table 5. The new vessels resolved in 70% of cases (27 eyes)

Table 1 Fluorescein angiographic features on presentation

	No. of eyes
Significant capillary closure (at least 1 quadrant)	15
Diffuse microvascular leakage	24
Venous leakage	12
Cystoid macular oedema	8
Branch vein occlusion	7

Table 2 Treatment given

	No. of patients
Topical steroids	24
Systemic steroids	7
Systemic steroids and immunosuppressives	6
Systemic steroids and photocoagulation	10
Photocoagulation alone	1
No treatment	2

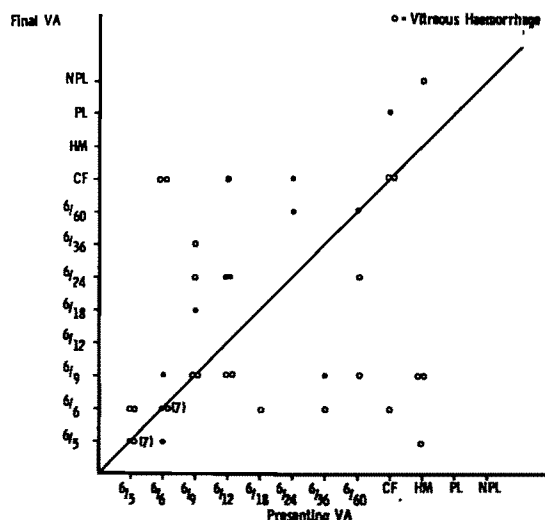


Fig. 5 Change in visual acuity during study period comparing patients with and without vitreous haemorrhage.

following treatment (medical and/or surgical), but in nine eyes the neovascular process was unaffected by treatment, and in three eyes assessment was not possible due to poor visibility.

Discussion

Neovascularisation is a fundamental element of the postinflammatory healing process in all parts of the body, and continues for as long as the appropriate angiogenic stimulus is present. In the eye such stimuli have been suggested to arise from hypoxic retina,³⁻⁸ inflamed retina,¹⁰ or from inflammatory cells themselves.¹¹ Previous series examining the natural history of new vessels in ocular inflammatory disease are few. The original paper by Eales¹² described young men with repeated intraocular haemorrhage, distended tortuous retinal veins, and retinal haemorrhages.

Table 3 Complications arising during treatment

	No. of eyes
Cystoid macular oedema	7
Persistent vitreous haemorrhage	2
Traction retinal detachment	2
Cataract	1

Table 4 Incidence of cystoid macular oedema (CMO)

	CMO	No CMO
Not associated with photocoagulation	2	22
Associated with photocoagulation	5	7

$\chi^2 = p < 0.01$.

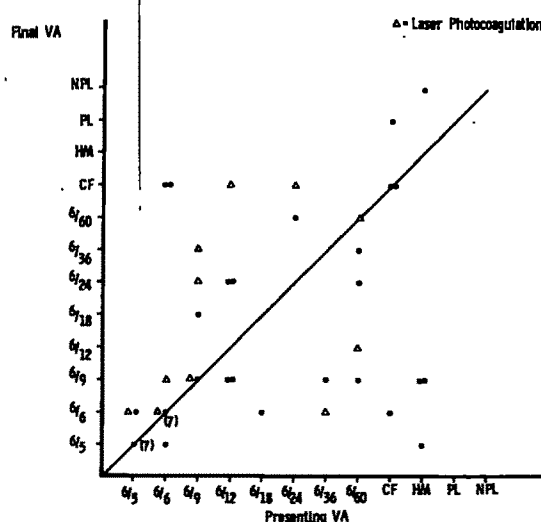


Fig. 6 Change in visual acuity during study period comparing patients who received laser photocoagulation with those who received only medical therapy.

The natural history was not recorded in what was presumably a heterogeneous group of diseases. Felder and Brockhurst¹³ reported 15 patients with intermediate uveitis who developed new vessels at the disc (three patients), and Spalton and Sanders¹⁴ reported on eight patients with sarcoidosis and retinal neovascularisation—six at the optic disc and two in the periphery associated with branch vein occlusion. Two of these are included in the present series and were treated by panretinal photocoagulation. The new vessels regressed in one, but the other developed macular oedema following treatment.

The present study has shown the clinical and angiographic features found in 39 eyes of 26 patients with neovascularisation due to posterior uveitis, and has attempted to assess their progress in response to medical and laser treatment. It is evident that such neovascularisation occurs in younger patients, and that the visual prognosis, even in the presence of significant vitreous haemorrhage, is good. In the majority of patients intraocular inflammation subsided on medical treatment, and in half of these

Table 5 Fate of new vessels

	No. of eyes
New vessels regressed on no treatment	1
New vessels regressed on medical treatment only	16
New vessels regressed on laser treatment only	1
New vessels regressed on combined medical and laser treatment	9
New vessels unaffected by all treatments	9
State of vessels unassessed (vitreous haem/cataract)	3
Total	39

patients this was sufficient to cause regression of the fronds, regardless of the aetiology of their uveitis. It is also noteworthy that one patient who never received systemic treatment also showed regression of new vessels with a reduction in intra-ocular inflammation.

The role of laser photocoagulation is less clear. In this series direct ablation of neovascular fronds was not attempted, though this regimen has been reported with good results.¹³ The only patient who received laser photocoagulation alone responded well, but the new vessels were peripheral in a small patch of minimal capillary closure and may have settled despite treatment. Laser treatment frequently caused regression of new vessels, but the high incidence of subsequent cystoid macular oedema, especially in those patients with significant capillary closure, was unexpected. Major series discussing the role of photocoagulation in the presence of non-inflammatory ischaemic conditions, such as diabetes, have shown the benefit of this treatment and the low incidence of subsequent macular oedema,¹⁵ though this complication is becoming more recognised.¹⁶ The visual prognosis was generally good in these patients, in contrast to patients with ischaemic proliferative retinopathy. Notably, traction retinal detachment, a common complication of proliferative diabetic retinopathy (51% of untreated cases),¹⁵ was rare in this series. This may be because of the transient nature of the vessels and that in all eyes examined a posterior vitreous detachment was present, thus excluding a scaffold on which new vessels could grow.

The pathogenesis of neovascularisation in the eye is unknown. However, there is increasing evidence that factors present in retinal tissue may stimulate angiogenesis, while others in the vitreous will inhibit it. In posterior uveitis there are three sources of possible angiogenic factors. Capillary closure, and thus hypoxic retina, occurs in this disease. This is often associated with branch vein occlusion, which has been shown in a number of conditions to be positively correlated with the development of new vessels.⁶ Retinal capillaries which have damaged endothelium leak and may be stimulus for neovascularisation.¹⁰ The disruption of the retinal vascular network is exemplified by the fluorescein angiograms of many patients which show diffuse microvascular leakage. However, this hypothesis has been challenged on the grounds that neovascularisation is not a feature of many retinal vascular diseases where there is persistent intraretinal oedema, for example. Coats' disease or diabetic maculopathy.¹⁷ Lastly, it has been proposed¹⁸ that the inflammatory cells themselves, either a subpopulation of stimulated T-lymphocytes¹⁹ or macrophages,²⁰ produce soluble factors (for example, lymphokines) which are

angiogenic. The latter hypothesis is particularly attractive in the case of posterior uveitis, where new vessels may appear regardless of the state of the underlying retinal vasculature and regress with adequate control of the inflammation.

This study indicates that retinal neovascularisation associated with ocular inflammation behaves in a different manner from retinal neovascularisation not associated with ocular inflammation. The visual prognosis is better in the presence of intraocular inflammation, and this is also true for vitreous haemorrhage. We would recommend that full and adequate medical treatment should be used to suppress the intraocular inflammation, with laser photocoagulation being reserved for further treatment once the eye is quiet and if recurrent vitreous haemorrhages occur.

We thank Mr Richard Dewhurst for preparing the illustrations and Miss Josephine Lacey for typing the manuscript.

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Combined occlusion of the central retinal artery and central retinal vein following blunt ocular trauma: a case report

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SUMMARY A healthy young woman suffered complete loss of the vision of one eye following a blunt ocular injury. She sustained a combined occlusion of the central retinal artery and central retinal vein of the affected eye. Initially few retinal haemorrhages were present, but they increased considerably in number and size during the day following injury.

Occlusion of the central retinal artery, the central retinal vein, or branches of these vessels, are well recognised events. Combined simultaneous occlusion of the central retinal artery and central retinal vein occurs very rarely, and has generally been observed in patients with systemic disorders such as leukaemia.¹ We report a case of a young woman who suffered a combined retinal vascular occlusion following blunt trauma to one eye. To our knowledge this is the first time that such a sequence of events has been recorded.

Case report

A 28-year-old woman was jabbed in the left eye by a finger during an altercation. She experienced immediate and total loss of the vision of this eye. She was in good health, and she had no past history of ocular disease.

One hour after this injury she attended the casualty department of the Glasgow Eye Infirmary, where her right visual acuity was found to be 6/6 unaided, and the left was no perception of light. No abnormality of the right eye was detected. The left eyelids were mildly bruised. There was a linear conjunctival laceration 1.5 cm in length, above and parallel to the limbus. No perforation of the cornea or sclera was found. The ocular media were clear. The left pupil was round, and reacted consensually but not directly to light. The intraocular pressure of each eye was 12 mmHg. There was no proptosis of the left eye.

The left optic disc was abnormally pale, and the retinal arterioles were extremely narrow. There was a cherry-red spot at the macula. The retinal veins were grossly engorged, with segmentation of the vascular column. A few small perivenous haemorrhages were seen.

Initial treatment consisted of intravenous acetazolamide 500 mg, and carbon dioxide rebreathing, on the assumption that the blunt injury might have induced central retinal arterial spasm.

After a further 30 minutes the left vision remained no perception of light. The left ocular pressure had fallen to 6 mmHg. The retinal arterioles remained very narrow. The retinal haemorrhages had increased considerably in both number and size.

During the following day there was a further increase in the number of retinal haemorrhages, with the formation of some preretinal haemorrhages. The left optic disc became grossly swollen (Fig. 1).

Fluorescein angiography, performed on the day after injury, confirmed the absence of perfusion of the left central retinal artery and vein. Choroidal perfusion was maintained. Later frames of the angiogram showed slight filling of the proximal retinal arterioles (Fig. 2).

The patient subsequently failed to regain any vision in the left eye.

Discussion

Simultaneous occlusion of both the central retinal artery (CRAO) and the central retinal vein (CRVO) is a rare event. Occasional reports show it has been observed in association with disorders such

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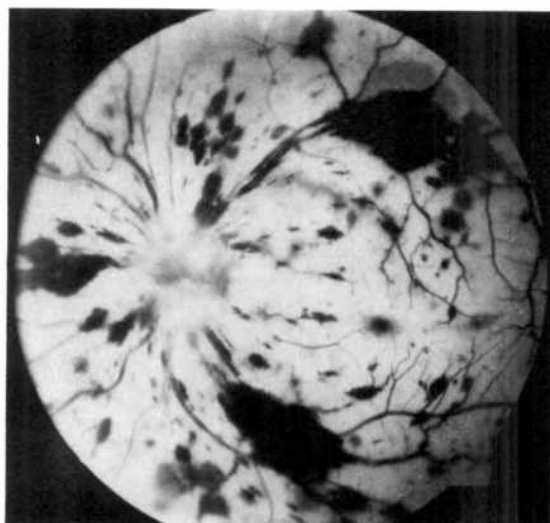


Fig. 1 Photograph of the posterior pole of the left eye one day after injury.

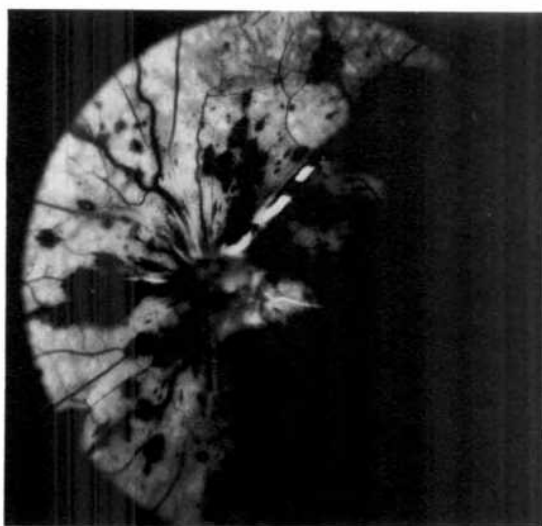


Fig. 2 Fluorescein angiogram frame of the left eye one day after injury (146 seconds after injection).

as leukaemia,¹ Behçet's disease,¹ septic cavernous sinus thrombosis,¹ subacute bacterial endocarditis,¹ systemic lupus erythematosus,² syphilis,³ and temporal arteritis.⁴ It is possible that in some of these cases the arterial and venous occlusions may not have occurred simultaneously.

Richards¹ collected six cases of combined retinal vascular occlusion and described a characteristic clinical picture. His patients suffered a rapid reduction of the vision of one eye, often progressing to no light perception within a few days. They all experienced some retrobulbar pain. In each case the optic disc was swollen, with peripapillary retinal haemorrhages. The retina was pale, with a macular cherry red spot. A paucity of haemorrhages was noted in the peripheral retina, and Richards contrasted this with pure CRVO, in which retinal haemorrhages are usually more widespread. Fluorescein angiography showed lack of flow in the retinal vessels, with preservation of the choroidal circulation.

Our case differs from this description in several respects.

Timing of visual loss. In Richards's series, and in other reports,^{2,5} visual loss occurred over hours, and in some cases vision continued to deteriorate for several weeks. Our patient suffered complete loss of vision of the affected eye from the time of her blunt ocular injury. This may have been because the CRAO was more complete, or it may have been the result of an associated optic nerve injury.

Aetiology. The combination of CRAO and CRVO has previously been reported in eyes of patients with

systemic disorders, particularly leukaemia. To our knowledge there is no previously recorded instance of a healthy patient suffering a combined central retinal vascular occlusion after blunt ocular trauma.

Fundus changes. All of Richards's cases had haemorrhages round the optic disc, with relative sparing of the peripheral retina. By contrast in our case retinal haemorrhages were initially few and scattered, but they increased over the ensuing 24 hours until florid retinal and preretinal haemorrhages involved in all regions of the fundus.

Other reports^{2,3,6} do not accord with Richards's fundus description. Bender⁶ described the case of a woman who suffered a combined retinal vascular occlusion 36 hours after a tooth extraction. On the morning that vision was lost, 'blurring of the right disc with profuse haemorrhages, exudate, and oedema throughout the retina' was observed.

During his investigation of the role of arterial ischaemia in retinal vein occlusion Hayreh reported the results of several series of experiments in which retinal arteries and/or veins of monkeys were occluded. He found that simultaneous occlusion of both central retinal artery and vein within the orbit by diathermy produced an initial picture of retinal pallor, with no blood flow within retinal vessels.⁷ Haemorrhages later developed in all three animals treated in this way. These were greatest round the optic disc or macula, and in one animal they were described as 'massive' and 'extensive'. This description bears similarities to the sequence of fundal changes in our clinical case.

In a later series of experiments Hayreh and

colleagues repeated the occlusion of the central retinal vein and artery in the orbit of 11 monkeys.⁸ On this occasion they found 'mild ischaemic odema ... associated with a few small venular haemorrhages (in one quarter)' though they noted that in one animal the retinal haemorrhages were far more numerous.

It is likely that combined CRAO and CRVO can produce widely differing patterns of clinical presentation and fundal signs depending upon such variables as (1) the relative severity of the arterial and venous occlusions; (2) the time course during which any arterial circulation is re-established; (3) the clinical condition producing the occlusions (for example, some of Richards's patients had lymphoma or leukaemia, and malignant infiltration may have contributed to the retinal pallor observed); (4) the patient's (or experimental animal's) age, since younger subjects may have a milder haemorrhagic response to retinal venous occlusion.

MECHANISM

The mechanism by which this combined retinal vascular occlusion was induced remains speculative. Haemorrhage within the optic nerve sheath can compress the nerve sufficiently to impair axonal transport. Jonasson and Cullen reported such a case caused by diving, in which the intrasheath haematoma also produced proptosis of the globe, and it mildly reduced vision.⁹ In our case the instantaneous loss of vision, the lack of proptosis, and the occurrence of a combined retinal vascular occlusion before the optic nerve head became swollen argue against such a mechanism.

There are a number of reported instances in which blunt ocular trauma has produced damage to the optic nerve, sometimes with degrees of nerve

avulsion from the globe.¹⁰⁻¹³ Severe ocular rotation has been cited as the cause of the optic nerve injury.^{10,13} It is possible that extreme rotation induced by the finger jab may have produced damage to or haemorrhage in the retrolaminar part of the optic nerve in our patient. This in turn may have compressed or disrupted the central retinal vessels within the nerve.

We thank Mrs J Murray and Mrs S Mitchell for secretarial assistance, Mrs A Currie for photographs, and Dr G N Dutton for his permission to report this case and for his helpful comments.

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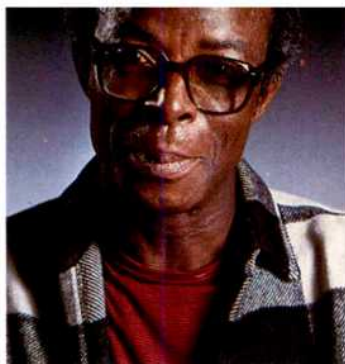
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Natural history of retinopathy of prematurity

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SUMMARY Sixty-nine infants at risk of developing retinopathy of prematurity (ROP) were entered into a prospective study to assess the incidence and natural history of the disease. Seventeen infants developed ROP, and in six eyes the disease progressed to stage IV ROP. The natural regression of a pupillary membrane and physiological vitreous haze was not influenced by the onset of ROP. Progression from stage I to stage III was rapid and the rate was influenced by the zone affected. Congestion and tortuosity of vessels in the posterior pole always signified stage III ROP. Progression from stage III to stage IV ROP was slower; it was characterised by the development of vitreoretinopathy, signified by the sudden onset of a vitreous haze. Iris congestion associated with poor mydriasis may be a grave sign indicating imminent retinal detachment. Cicatricial ROP can be divided into retinal and vitreoretinal cicatricial disease directly related to the stage of active disease reached. ROP is characterised by its self limiting nature, but the stage at which it becomes inactive varies and will influence the final outcome.

Retinopathy of prematurity (ROP) remains a persistent problem threatening visual development to a greater or lesser extent in the premature infant.¹ With the advent of vitreoretinal surgery successful anatomical results have been reported in eyes with advanced cicatricial disease.² The functional success in these eyes is doubtful, and whether surgery should be advised in such cases may pose an ethical question. A renewed interest has developed in the treatment of ROP by cryosurgery during the active stage of retinopathy.³⁻⁵ One of the problems experienced with cryosurgery is the lack of specific selection criteria for treatment at the appropriate time. The typical retinal changes characteristic of ROP and their evolution have been well reported in the past.^{6,7} Nevertheless we still have a poor understanding of the natural history of the disease and cannot explain the striking phenomenon of spontaneous regression. A better understanding of the disease is of fundamental importance if treatment of it in the acute stage is planned in the future. We report our experience of the natural history of ROP.

Materials and methods

Sixty-nine patients at risk of developing ROP

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admitted to the Neonatal Intensive Care Unit at the Hammersmith Hospital between May 1983 and February 1985 were entered into a prospective study to determine the incidence and natural history of the disease. The criteria for selecting high risk infants were the following: infants with a gestational age below 30 weeks and/or a birth weight below 1500 g. All other infants admitted to the unit during the study period not fulfilling these criteria and exposed to oxygen were also examined, but none of them developed ROP.

Eye examination was scheduled at three weeks after birth if the infant's condition allowed, and it was repeated at weekly intervals by one of the authors (WES) as long as the infant remained in the Intensive Care Unit. Selected infants were examined at more frequent intervals—that is, progressive stage III ROP on serial examination. Mydriasis was achieved by the instillation of phenylephrine 2.5% drops and cyclopentolate 1% drops one hour and 30 minutes before examination. The fundus was examined by indirect ophthalmoscopy with the aid of a 28 dioptre lens and scleral indentation only where indicated—that is, to differentiate between zone II and zone III disease or where inadequate information was obtained without indentation. We found that scleral indentation was essential whenever the infant speculum was used, resulting in blepharospasm and a Bell's phenomenon. When the lids were prised open

by the examiner, blepharospasm was not stimulated and adequate information could be obtained with a little patience. This technique was also followed with fundus photography, and no sedation was required. Retinal changes were recorded with a Zeiss fundus camera in selected eyes only.

After discharge the infants entered into the study were re-examined in the outpatients department at regular intervals. Ocular findings associated with prematurity were recorded and included the presence of a pupil membrane (*tunica vasculosa lentis*) and a physiological peripheral vitreous haze.

ROP changes were recorded in accordance with the international classification as soon as it became available. Stage I is characterised by the formation of a demarcation line, stage II by the formation of a retinal lesion with height and volume extending out of the retinal plane, stage III by an increase in height and volume of the retinal lesion associated with fibrovascular proliferation, and stage IV when retinal detachment develops. The retinal lesion is localised by dividing the retina into three zones centred round the optic disc. Zone I consists of a circle with the radius twice the optic disc-macula distance, zone II is more peripheral and extends from the edge of zone I to the edge of a circle with a radius of the optic disc-nasal-ora distance, and zone III is a crescent peripheral to the edge of zone II and does not involve the nasal 3 clock hours of the retina.⁸ Iris vascular changes and changes in pupil dynamics associated with ROP were recorded.

The time of onset was recorded when a demarcation line developed. As regression is a gradual process, it was difficult to be precise about the time it started. Thus, in relating the age of the infant to the stage of ROP, the age at which the maximum stage ROP had developed was used instead of the age at regression, to enable more accurate comparison between individual eyes. Infants whose eyes reached stage III plus with no evidence of regression on serial examination were entered into a paired eye study to assess the value of cryosurgery, the results of which will form part of a future study. Selection of these cases for cryosurgical treatment was based on the experience of Kingham previously reported.⁹ The control eye only was considered to the end stage of ROP in this study on the natural history, and all treated eyes excluded as soon as treatment was applied.

Results

INCIDENCE

Of 69 high risk infants 17 (24.5%) developed some degree of ROP. All cases were bilateral and sym-

metrical with the exception of two cases. In one of these the more severely affected eye had a persistent posterior hyaloid artery, and, in the second, one eye progressed to stage III and the second eye to stage II ROP only. In 34 eyes visual function was lost in seven, five of which did not receive cryosurgery, and the natural history could be followed from the time of onset to advanced cicatricial disease with a total retinal detachment. These included one case with bilateral zone I ROP and three control eyes with zone II ROP. One infant with zone I ROP was too ill to be considered for cryosurgery and eventually died at the age of 4 months. In 11 out of 17 infants no retinopathy was present at the initial examination.

PUPILLARY MEMBRANE AND VITREOUS HAZE

In 28 out of 34 eyes that eventually developed ROP a pupillary membrane was present at the initial examination. A physiological peripheral vitreous haze was present at the initial examination in 20 out of 34 eyes and cleared within four to five weeks after birth. The mean age at which regression of the pupillary membrane and peripheral vitreous haze took place was equal for both the ROP and non-ROP groups.

RETINAL VASCULAR CHANGES

In four eyes of two infants the onset of a demarcation line was observed to be preceded by dilatation and increased tortuosity of peripheral capillaries directly behind the margin of vasogenesis. A demarcation line (stage I) developed within one to two weeks thereafter in these eyes. Since the conclusion of this study we have observed that these minor vascular changes were present in the majority of eyes that developed ROP and probably always precede the onset of stage I as defined. These changes may regress and do not necessarily indicate the onset of ROP. The low incidence reported in this study does not represent the true incidence, as it did not form part of the data collection sheet and was thus not specifically documented. It was added late in the study and referred to as 'pre-ROP' changes. In eight eyes of four infants, including one who finally progressed to end stage ROP in both eyes, fine capillaries were identified on the retinal surface directly behind the demarcation line one week after diagnosis. These capillaries were fragile and gave rise to small preretinal haemorrhages in three of the eight eyes (Fig. 1). None of the eyes in this study developed a temporary retinal detachment of non-vascularised retina.

Progression to stage II ROP was characterised by the early development of a retinal shunt lesion with an associated progressively increasing congestion and tortuosity of the peripheral retinal vasculature,

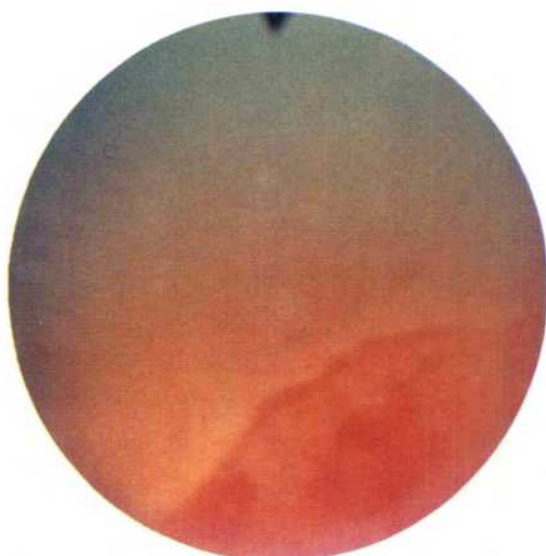


Fig. 1 Stage I ROP with a preretinal haemorrhage from abnormal surface retinal capillaries.

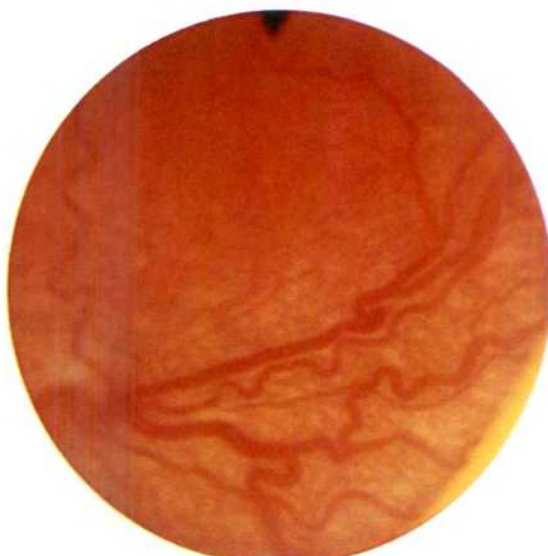


Fig. 2 Zone II stage III ROP with characteristic posterior pole congestion and increased retinal vascular tortuosity.



Fig. 3 Globular shunt lesions extending posterior towards the optic disc. Zone II Stage III ROP.

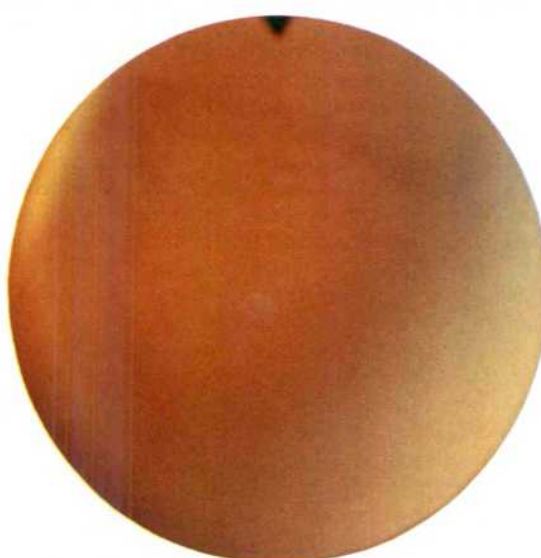


Fig. 4 Vitreous haze preceding retinal detachment and signifying the onset of vitreoretinopathy. Zone II stage III plus ROP.

slowly extending further posteriorly towards the posterior pole.

Congestion and tortuosity of the retinal vasculature increased proportionately to the increasing size of the retinal shunt lesion. Such involvement of the posterior pole and optic disc always indicated stage III ROP (Fig. 2) as previously reported.^{6,7} In progressive stage III ROP the retinal shunt lesion was

seen on serial examination to increase in volume and develop a fibrovascular component at the base of the lesion that projected into the vitreous perpendicular to the retina. One case with zone II stage III ROP also developed multiple globular shunt lesions on the retinal surface posterior to the main circumferential lesion in both eyes (Fig. 3). This clinical appearance has been well documented.¹⁰

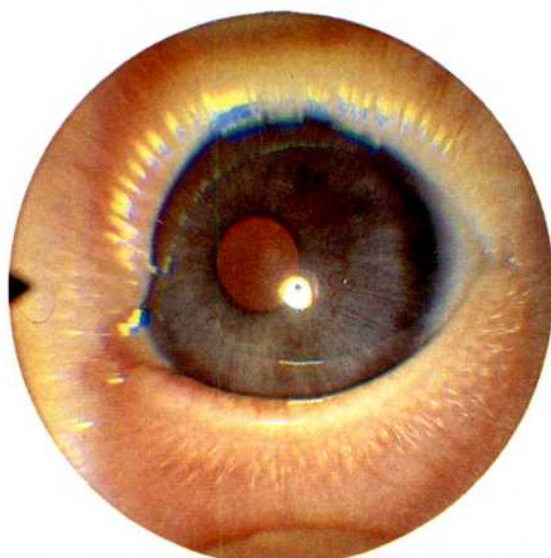


Fig. 5 Iris congestion with poor mydriasis. Zone II stage III plus ROP.

VITREORETINOPATHY

Six eyes progressed to stage IV ROP and included two zone I, one zone III, and three zone II retinopathy eyes. In the three untreated zone II eyes, and both the zone I eyes that progressed to stage IV, retinal detachment was preceded by the sudden onset of a vitreous haze one week before retinal detachment developed (Fig. 4). This characteristic vitreous change was associated with a small intragel haemorrhage from one of the retinal lesions in one eye. Clinical evidence of forward traction on the retinal shunt lesion was clearly defined by the configuration of the blood in the vitreous. This eye finally progressed to a total retinal detachment. This vitreous change was not observed in the zone III eye that progressed to retinal detachment but would have been missed if it was present and localised to the affected temporal retina.

IRIS CHANGES AND PUPIL DYNAMICS

Iris congestion with a poor response to mydriatics developed in five eyes, three zone II and two zone I eyes, with progressive stage III ROP on serial examination (Fig. 5). All five of these eyes progressed to stage IV ROP with extensive retinal detachment.

RETINAL CHANGES IN REGRESSION

Regression was characterised by a decrease in retinal vascular congestion and tortuosity associated with a simultaneous decrease in volume of the retinal shunt lesion. The formation of a 'brushborder', as previously reported by Flynn *et al.*,⁶ often coincided

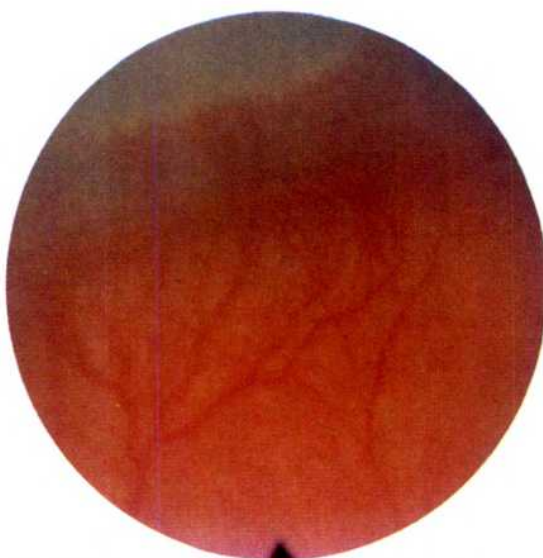


Fig. 6 'Brushborder' characteristic of early regression.

with, or followed shortly after this vascular decongestion, signifying a return to normal retinal vasogenesis (Fig. 6). The newly forming retinal vasculature peripheral to the site of the retinal shunt lesion had a characteristically stretched or wishbone configuration which was distinctly different from the normal retinal vasculature as previously reported.⁶ In one infant this second phase of retinal vascularisation became arrested for two weeks in both eyes when a temporary second demarcation line formed.

In the five eyes that progressed to extensive retinal detachment the retinal shunt tissue decreased in volume and changed in colour from a characteristic orange to yellow soon after retinal detachment had developed. Coinciding with this process a simultaneous transgel traction developed, pulling the retina (rim of purse string) up against the posterior lens surface. At this open funnel stage of retinal detachment it seemed to be purely tractional in origin. Exudative detachment followed two to three weeks later when the retinal detachment changed in character to a bullous closed funnel retinal detachment. No retinal breaks were observed in any of the reported eyes.

STAGE ROP RELATED TO AGE OF INFANT FOR ZONES I, II, AND III

The age at onset of ROP was similar for the three zones, with an average age of 6.5 weeks. Further progression had a striking similarity in all three zones, with a relatively rapid development up to stage III, followed by a relatively long interval between the onset of stage III and progression to

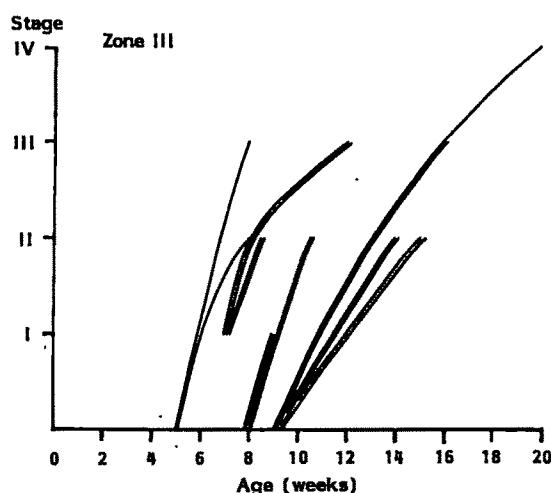
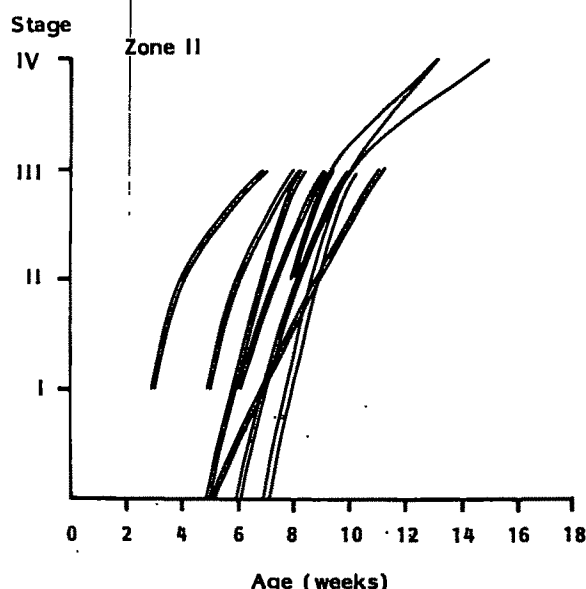
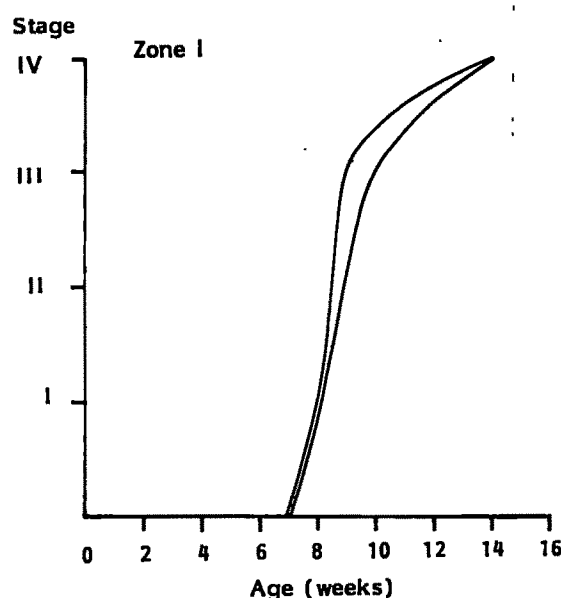


Fig. 7 Age of infant (weeks) related to the stage of ROP for zones I, II, and III.

Table 1 Mean duration of ROP in weeks for zones I, II, and III at the different stages of evolution of the retinal lesion

<i>Zone I</i>			
Age at onset in weeks	Stage I 7.5 (2)*	Stage III 10 (2)	Stage IV 14.5 (2)
Time interval in progression	Stage I Stage III	to III to IV	2.5 weeks 4.5 weeks
Overall duration active ROP	7 weeks		
<i>Zone II</i>			
Age at onset in weeks	Stage I 6.6 (16)	Stage III 9.6 (16)	Stage IV 13.6 (3)
Time interval in progression	Stage I Stage III	to III to IV	3 weeks 4 weeks
Overall duration active ROP	7 weeks		
<i>Zone III</i>			
Age at onset in weeks	Stage I 7.5 (16)	Stage III 12.9 (5)	Stage IV 20 (1)
Time interval in progression	Stage I Stage III	to III to IV	5.4 weeks 7.1 weeks
Overall duration active ROP	12.5 weeks		

*Number of eyes in parentheses.

stage IV ROP (Fig. 7, Table 1). However, in general, progression to stage III was more rapid in zone I ROP and slowest in zone III ROP, with a duration of 2.5 weeks in zone I, 3.0 weeks in zone II, and 5.4 weeks in zone III before stage III was reached. Progression from stage III to stage IV ROP followed after a duration of 4.5 weeks in zone I, 4.0 weeks in zone II, and 7.1 weeks in zone III ROP. The mean overall duration before the maximum stage was reached was 7.0 weeks for zones I and II and 9.4 weeks for zone III ROP. The number of eyes included in this study was too small to allow statistical analysis, but confirms a trend in the rate of development through the different stages for zones I, II, and III.

Table 2 Retinal sequelae in infants in whom the disease process did not progress beyond stage III ROP

Retinal sequelae	Case no.						
	1	2	3	4	5	6	7
Optic disc dragging	+		+	+	+		
Pre-retinal fibrosis		+					+
Wishbone vessels		+			+	+	+
Increased tortuosity		+	+			+	+
Zone	III	II	II	III	III	II	II
Stage (maximum)	III	III	III	III	II	III	III

SEQUELAE

Permanent retinal sequelae were recorded in seven infants who did not progress to stage IV or vitreoretinal ROP (Table 2). These findings were recorded at the age of 6 to 18 months when co-operation was poor and accurate clinical examination of the fundus difficult. The reported results may thus not be an accurate representation of the true incidence of permanent retinal sequelae in this group. Retinal changes were related either to the retinal vasculature or to residual fibrous tissue on the retinal surface at the previous site of a retinal shunt lesion, with or without associated surface traction on the retina. Of the five eyes that progressed to vitreoretinal ROP, and finally developed a total retinal detachment, all developed microphthalmos with anterior displacement of the iris-lens diaphragm and shallowing of the anterior chamber. In one infant with zone II ROP and an obliterated anterior chamber band keratopathy developed in both eyes.

Discussion

No cases of ROP presented outside the defined group of high risk infants, so the adopted criteria were accurate in identifying infants at risk of developing ROP.

Vascular congestion in the posterior pole was confirmed as an important clinical sign which acted as an indicator of the activity of the shunt lesion and indicated whether it was still in an active phase. Similarly, decreased congestion and tortuosity indicated early regression. These characteristic posterior pole changes may thus be a helpful clinical sign to paediatricians screening infants for ROP who may not be familiar with the indirect ophthalmoscope and scleral indentation, necessary for accurate grading. Furthermore, iris congestion associated with a poor mydriatic response should be regarded as a warning sign that the disease process has reached an advanced stage, when further progression to stage IV becomes a real danger.

From the observations made in this study it became evident that the disease process in ROP is self

limiting, with a clinically identifiable time of onset and an end stage when the disease process becomes inactive regardless of the stage of ROP previously reached. Permanent retinal sequelae are directly related to the maximum stage reached. In advanced ROP, stage III and stage III plus, the severity of cicatricial ROP will depend on whether or not vitreoretinopathy had developed. In eyes where the disease remained confined to the retina only, cicatricial ROP will be limited to relatively minor preretinal fibrosis and associated surface tractional retinal changes. Those eyes that continue to progress after stage III had been reached will ultimately develop vitreoretinopathy with severe consequences. Mousel reported a similar vitreous change in one case but referred to it as an 'inflammatory reaction'.¹¹ Cicatricial disease is characterised by extensive tangential and transgel retinal traction and invariably progresses to extensive retinal detachment and blindness in zones I and II ROP. In zone III disease it is confined to the temporal periphery only and will result in varying degrees of temporal retinal drag related to the stage and volume of the retinal lesion at the time of regression. A localised temporal retinal detachment may develop in these eyes. It would thus be practical to classify cicatricial disease in two main categories, retinal and vitreoretinal cicatricial disease (Fig. 8). Infants at risk of developing ROP should be screened at regular intervals after the age of 4 weeks. In cases that had progressed to stage III ROP serial examination by the same clinician is of fundamental importance to identifying early signs of either regression or progression if cryosurgery is planned.

A critical stage is reached at three to four weeks after the onset of stage III ROP, especially in zone I and II ROP, where a higher incidence of a more advanced stage disease can be expected. If no sign of

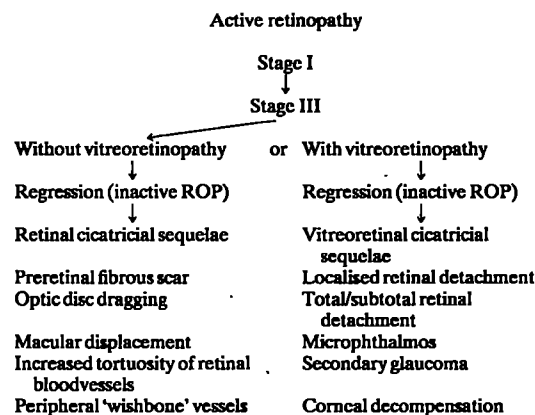


Fig. 8 A schematic representation of the development of cicatricial ROP.

regression can be detected on serial examination at this stage, a real danger of further progression to vitreoretinopathy exists, and cryosurgical intervention should be considered.

A better understanding of the natural history of ROP may enable us to establish more accurate selection criteria in eyes considered for cryosurgical intervention. Not only will this enable us to assess the effectiveness of cryosurgery more accurately, but also prevent unnecessary treatment in future.

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Glaucoma in Fuchs' heterochromic cyclitis associated with congenital Horner's syndrome

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SUMMARY We report a retrospective study of five patients with monocular Fuchs' heterochromic cyclitis associated with an ipsilateral Horner's syndrome. The minimum follow-up was 10 years. The presenting findings were cyclitis in three of the patients and heterochromia iridis associated with blepharoptosis in the other two. The major factors affecting all five patients were cataract and glaucoma. The intraocular pressure was uncontrolled even with maximal therapy, and anti-glaucomatous surgery was performed in all cases. A short period of good postoperative control was followed by an intractable ocular hypertension, causing loss of useful vision in all patients. The remarkable combination of Horner's syndrome with glaucoma and their interaction is discussed.

Fuchs' heterochromic cyclitis (FHC) is a commoner ocular disorder than has generally been recognised.¹⁻⁹ It is frequently overlooked when the heterochromia is slight or when all its clinical features are not present at the same time.

One of the most serious complications of the disease is glaucoma, which has been observed in 18.6% of the studied cases.⁶ Although there is no unanimity on the prognosis for the glaucoma in this syndrome,^{3,7} recent communications^{8,10} suggest that it usually becomes resistant to medical therapy, and surgery is only moderately successful.

The purpose of this report is to describe the manifestations of unilateral FHC associated with Horner's syndrome and complicated by ipsilateral glaucoma in five patients. To the best of our knowledge, no similar cases have been previously reported. We discuss the significance of the association and the implications regarding the unfavourable course of the glaucoma in these patients.

Case reports

CASE 1

A 53-year-old male was first seen in May 1970 because of a progressive decrease in visual acuity, elevated intraocular pressure (IOP), and recurrent

inflammations in the left eye during the preceding three years. Drooping of the eyelid and discoloration of the iris had been evident in the affected eye since early childhood.

His best corrected visual acuity was 6/7 (20/25) in the right eye (RE) and limited to light perception in the left eye (LE). The intraocular pressure (IOP) in the LE while the patient was on 4% pilocarpine and acetazolamide 250 mg was 28 mmHg. The IOP in the RE was 14 mmHg, and when the patient was submitted to a provocative topical dexamethasone test the eye did not react with a significant rise in tension.

External examination of the LE revealed 2 mm blepharoptosis. Slit-lamp biomicroscopy disclosed a normal RE and a few white keratic precipitates (KP) with flare and cells in the anterior chamber in the LE. The right iris was brown and rich in crypts in marked contrast to that of the left eye, which was light grey, without crypts, and showed transillumination throughout an extensive depigmented area. Gonioscopy showed a few engorged blood vessels in the LE and wide open angles in both eyes. Ophthalmoscopic examination showed a normal right fundus, whereas visualisation in the LE was impossible owing to an almost mature cataract.

Two weeks after discontinuation of topical anti-glaucoma medication both pupils reacted to light and accommodation, and miosis of 1.5 mm was disclosed in the LE; 4% cocaine hydrochloride failed to dilate the left pupil but fully dilated the right. Marked left

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pupillary dilatation was observed after further instillations of 1% epinephrine.

In January 1972 cyclodialysis was performed in the LE because of uncontrollable IOP despite supplementary medication. After an apparently good postoperative period of three months the IOP increased progressively to 30 mmHg despite resumption of medical therapy.

After an uneventful left intracapsular extraction carried out in April 1972, which restored the vision to 6/10, a 0-40 glaucomatous cupping and involvement of the inferior temporal rim were noticed. The left visual field showed a small step. In March 1977 trabeculectomy was performed because of further deterioration in the left visual field. A 2 mm hyphaema was noted after the operation. Transient good postoperative control of the IOP was followed by persistent elevation to 35 mmHg. The patient was not seen again until 1984, when the IOP in the LE was uncontrolled despite maximum medical therapy. The optic disc was totally cupped, and the visual field was reduced to 'tubular', with an additional isolated temporal island. The RE remained normal.

CASE 2

A 51-year-old female was referred for consultation in January 1973 because of a history of recurrent inflammation and decreased vision in the LE. During the previous 10 months the affected eye had developed ocular hypertension, and 4% pilocarpine and prednisone were administered.

On examination her corrected visual acuity was RE 6/6 (20/20) and LE counting fingers. The IOP was 25 mmHg in the LE (under topical medication) and 15 mmHg in the RE. The RE was normal, and its IOP did not react to topical steroid testing.

The left upper eyelid had 2 mm of blepharoptosis with good elevator function; a picture taken when the patient was 10 years old confirmed the presence of this abnormality since childhood. The right eyelid was normal.

Biomicroscopy disclosed typical FHC findings with a mature cataract in the LE. Gonioscopic examination revealed open angles with ciliary processes visible. A few large vessels were seen in the angle of the LE.

The left pupil was miotic and unresponsive to 4% cocaine (administered while the patient was off pilocarpine treatment for 10 days), but dilatation was observed after repeated instillations of 1% epinephrine. The right pupil reacted normally.

Uneventful left intracapsular cataract extraction was performed in January 1974 with subsequent improvement in visual acuity to 6/12 (20/40). At this stage both optic discs were normal.

During the following years the IOP in the LE

remained uncontrolled (32 mmHg) despite maximum medical therapy. The left optic disc became progressively damaged, and the visual field showed a significant superior nasal scotoma. In July 1978 trabeculectomy was performed, with subsequent bleeding into the anterior chamber. The hyphaema, not absorbed after seven postoperative days, required surgical removal. No filtering bleb developed, though the IOP decreased to 15 mmHg.

The patient was seen incidentally in April 1983 because of a traumatic corneal ulcer in the RE. The IOP was RE 14 mmHg and LE 30 mmHg despite maximally tolerated medical therapy. In the LE vision was reduced to 1/20, and the visual field consisted of a central zone connected by a narrow bridge to a temporal island due to a totally cupped optic disc.

CASE 3

A 60-year-old female presented in March 1975 with a 48-hour history of loss of vision in her painful RE. The patient claimed to have had a 'smaller' right eye and ipsilateral iris hypochromia since childhood. For many years she had received intermittent topical corticosteroids for chronic inflammation in the RE.

Ocular examination revealed visual acuity limited to light perception in the RE and 6/6 (20/20) in the LE. The anterior segment of the RE showed blepharoptosis of 2.5 mm, with the lower lid slightly higher than that of the left side. Biomicroscopy of the RE disclosed perikeratic congestion, hazy cornea, a few hyaline posterior deposits, turbid aqueous, a hypochromic iris, and a hypermature cataract. The LE was normal. Applanation tonometry values were RE 50 mmHg and LE 18 mmHg. On gonioscopy the angles were open. Right phakolytic glaucoma was diagnosed, and uneventful intracapsular cataract extraction was performed. After the operation the best corrected visual acuity in the RE improved to 6/9 (20/30), and the IOP dropped to 22 mmHg. The right optic disc had a deep cup with involvement of the inferotemporal rim and a corresponding visual field defect. The iridocorneal angle remained open all around without synechiae. A few months later the IOP progressively increased to 30 mmHg and remained at this level despite maximal medical therapy.

Cyclodialysis was performed in February 1976, but its hypotensive effect was only transitory. Six months later the IOP increased again to 32 mmHg despite maximal topical and systemic medication. In the 10 years' follow-up the IOP remained uncontrolled and the optic disc was progressively damaged. In the unaffected eye the IOP remained normal, and a dexamethasone test was negative.

The patient refused additional surgical treatment.

CASE 4

A 52-year-old woman was first seen in December 1971 because of a 14-year history of heterochromic cyclitis, cataract, and ocular hypertension in her RE. The ocular inflammation and the IOP responded favourably to topical therapy. The patient reported that the affected eye had been 'smaller' than the left eye ever since she could remember.

Slight enophthalmos and blepharoptosis of 2 mm with dropping of the lower lids was noted in the affected eye.

Best corrected visual acuity was RE 6/60 (20/200) and LE 6/7.5 (20/25). The IOP in the RE was controlled with 4% pilocarpine and acetazolamide 250 mg. The IOP in the LE was normal and did not react to topical corticosteroid testing.

Biomicroscopy of the RE disclosed a few dispersed KP and minimal flare in the anterior chamber. The iris was hypochromic, with a dull surface, and showing patchy areas of transillumination. Gonioscopically the angle was partially closed in the upper half but otherwise open to the ciliary body. A posterior subcapsular immature cataract was present. The optic disc seemed normal. The LE was absolutely normal.

The miotic right pupil, two weeks after discontinuation of topical medication, reacted normally to light and accommodation but failed to respond to a 4% cocaine test, whereas the normal opposite pupil dilated widely.

In June 1973 an uneventful extracapsular extraction in the RE followed by discission of a secondary cataract restored vision to 6/18 (20/60). After surgery slight atrophy of the optic disc was disclosed, and a nasal field defect was detected. The IOP was normal but after 10 months measured 30 mmHg despite maximally tolerated medical therapy. Cyclodialysis performed in April 1974 controlled the IOP for a period of eight months, but was followed by refractory ocular hypertension during the subsequent years. A Scheie filtering procedure performed in March 1977 was followed by hyphaema and had a hypotensive effect that lasted only a year after surgery.

In December 1984 a follow-up examination showed that the right optic disc was totally damaged, and the visual field was reduced to two temporal islands. The LE remained normal.

CASE 5

A 56-year-old male was referred to us in May 1974 because of a gradual decrease in visual acuity in the LE during the preceding three years. The patient had a long history of repeated episodes of inflammation, as well as a lighter coloured iris in that eye. He also reported that the left upper lid had drooped since his youth.

On ocular examination his best refracted visual acuity was RE 6/6 (20/20) and LE 6/24 (20/80). External examination of the LE revealed a blepharoptosis of 2.5 mm; slit-lamp biomicroscopy disclosed in the LE a few KP with filaments and a hypochromic iris. The normal crisp appearance of the iris was absent, and the iris surface was blurred. A transillumination defect of the iris and gaps in the pigment ruff were noted. Gonioscopy revealed an open angle with few dilated blood vessels. The lens showed an incipient subcapsular posterior cataract. A deep cup was noted. The IOP was 30 mmHg, and a small nasal defect was disclosed in the visual field.

The RE was completely normal. Its IOP was 12 mmHg, and the eye did not react to a provocative topical dexamethasone test.

Both pupils reacted normally to light and accommodation. Miosis of 1.5 mm was present in the LE. After instillation of 4% cocaine the left pupil remained unchanged, while the right pupil reacted with 5 mm dilatation.

Over a one-year period the IOP in the LE remained uncontrolled despite strong topical and systemic medication, and a significant progression in loss of visual field was disclosed. Trabeculectomy was performed in January 1976. Hyphaema occurred during surgery. No distinct conjunctival bleb developed postoperatively. The IOP remained controlled for nine months without medication. In May 1977 extensive rubeosis was noted, and the IOP increased to 36 mmHg despite the reinstitution of antiglaucoma medical therapy. The patient was lost to follow-up, but when he was last seen, in May 1984, the IOP in the LE exceeded 40 mmHg, and vision was reduced to temporal light perception only. The left optic disc was totally cupped. The RE remained normal.

Discussion

The distinctive features of FHC are slowly progressive uveitis with non-pigmented KP, minimal cells and flares in the anterior chamber, atrophy of the iris with hypochromia, and absence of posterior synechiae. The disorder is often associated with cataract and sometimes with glaucoma.

The aetiology of FHC is still subject to controversy. Some investigators consider that we are dealing with an immunological disease related to a defect in suppressor T-cell activity.¹⁰ Earlier theories pointed to the possible role of an initial infectious process.¹ More recent studies have demonstrated chorioretinal lesions, particularly suggestive of toxoplasmosis.^{11,12} The neurogenic theory of Passow¹³ proposed that damage to the sympathetic nervous system can mediate the changes in FHC; the pre-

sumption originates from the fact that sympathetic lesions due to neonatal injury may be followed by ipsilateral iris hypochromia. The hereditary theory⁶ originates from the fact that the more important types of iris heterochromia are hereditary in origin.

Horner's syndrome is an uncommon condition deriving from an interruption of the sympathetic pathway at any point along its course between the hypothalamus and the orbit. The syndrome accompanied by iris heterochromia usually indicates a long-standing cervical sympathetic denervation.

We report here a follow-up for 10 to 14 years of five patients with monocular FHC associated with ipsilateral Horner's syndrome and complicated by glaucoma. The diagnosis of FHC was based on the presence of the above mentioned features of the condition. The diagnosis of Horner's syndrome was based on the presence of blepharoptosis and miosis and the failure of the affected pupil to respond to 4% cocaine, whereas the opposite pupil dilated briskly. In every case Horner's syndrome was considered to be of congenital origin, as a 'smaller' eye had been noted since early childhood.

Cyclitis was the presenting sign of FHC in three patients (cases 2, 4, and 5) followed by iris hypochromia. In the two other patients (cases 1 and 3) heterochromia associated with blepharoptosis was the first apparent finding of the syndrome, occurring during youth and preceding other signs of uveitis by 20 to 30 years. In this regard O'Connor¹⁰ confirmed that a significant number of patients with FHC have iris heterochromia since birth or early childhood.

We believe that the detection of a previous ipsilateral Horner's syndrome, as in cases 1 and 3, suggests the possibility that sympathetic damage exerts a trophic influence on the development of iris hypochromia and perhaps mediates other changes in FHC. In cases 2, 4, and 5 both immunological and/or sympathetic mechanisms may be taken into consideration. In this connection Calmettes and associates¹⁴ reported a remarkable case in which Horner's syndrome following stellate ganglionectomy and FHC developed consecutively in the same eye.

Cataract was a major problem affecting all five patients in the current series: four patients developed posterior subcapsular cataract within four to 20 years after the first manifestation of FHC; in one patient (case 5) cataract was detected very early in the course of the disease. Four patients underwent uneventful cataract extraction (three intracapsular and one extracapsular) with prompt improvement in vision. In our experience the prognosis for cataract extraction in FHC is fair and the operation is no more likely to be complicated than any routine cataract surgery. The cyclitis was not worse after than before the operation. This confirms the good prognosis noted by

Franceschetti² and Smith and O'Connor¹⁵ but differs from the experience of Ward and Hart,¹⁶ Norn,¹⁷ and Liesegang,⁸ who found a high prevalence of hyphaema, extensive peripheral synechiae, corneal oedema, and persistent pupillary membranes. Our results also differ from the findings of Hart and Ward,¹⁸ which indicated that lens extraction has a deleterious effect on the dynamics of the IOP in eyes with FHC. Because previous patients with FHC who underwent extracapsular cataract extraction with posterior chamber lens implantation did not show a tendency to ocular hypertension,¹⁰ the use of this procedure seems advisable, especially in monocular cases.

The most serious complication in FHC remains the development of glaucoma. There has been a statistically significant increase in the incidence of this complication over the last 30 years. Whether the increase is merely an expression of improved diagnostic methods and better attention or is due to indiscriminate employment of topical steroids remains uncertain.

The cause of glaucoma in FHC is poorly understood. Huber³ considered the main cause of ocular hypertension to be an increase of the outflow resistance located in the trabeculum. Chandler and Grant¹⁹ stated that rubeosis of the iris in the anterior chamber angle induces the development of chronic secondary glaucoma.

In the current series all five patients with unilateral FHC had ipsilateral ocular hypertension resembling chronic open angle glaucoma in its course and symptomatology. One patient (case 3) presented with phakolytic glaucoma at the time of initial diagnosis, but after the cataract extraction extensive damage to the optic disc indicated also long-standing open angle glaucoma. The onset and duration of glaucoma varied: in one of the patients (case 4) glaucoma became evident concurrently with the appearance of cyclitis, while it was only a subsequent development in the remaining four patients. All patients developed glaucoma before cataract extraction.

There is no general agreement on the prognosis of glaucoma in FHC, and most authors report their conclusions on cases with a short control period. Some workers^{7,20} claimed a favourable outlook when the glaucoma was treated early. Other studies^{4,10} suggest that glaucoma usually becomes refractory to medical treatment. In the series reported by Liesegang,⁸ the prognosis was poorer than previously reported, although the author demonstrated success in controlling IOP by combined medical and surgical therapy in 21 of 32 patients.

In the current series maximum medical therapy (two topical agents with or without a carbonic

anhydrase inhibitor) and cataract extraction were unsuccessful in controlling the IOP. Therefore anti-glaucomatous surgery was performed in all cases: three patients (cases 1, 2, and 5) underwent trabeculectomy, one patient (case 3) cyclodialysis, and one patient (case 4) cyclodialysis followed by a Scheie filtering operation. None of these procedures, though performed correctly, presented a well formed functioning conjunctival bleb. Hyphaema was frequent, and immediate postoperative complications and extensive rubeosis developed in one patient (case 5) a few months after glaucoma surgery. In all cases surgical procedures resulted in a short-term hypotensive effect followed by intractable ocular hypertension. In some of these patients the vascular accidents appear to have compromised the surgical result.

The cases in our study were selected out of a large group of 56 patients with FHC who were under long-term observation at the same period. Eight additional cases were also complicated by glaucoma but were not associated with Horner's syndrome. Of these cases (two of them in the aphakic eye), the IOP could be kept under control with medical treatment in only one patient. Though the number of cases is small and statistically insignificant, it appears that in more than 90% of patients the glaucoma, if the follow-up period is prolonged, becomes completely refractory to any form of therapy and is eventually the cause of loss of useful vision. In this matter our experience is different from all statistics showing a better prognosis.

No IOP abnormalities were detected in the uninvolvement of patients in the present series. A provocative topical dexamethasone test was carried out in these eyes; only one fellow eye reacted with a significant rise in IOP and was classified as an intermediate steroid responder.

The remarkable combination of Horner's syndrome with glaucoma and their interaction seems inconsistent with what had been expected in such cases. The relationship between Horner's syndrome and IOP has been studied both in animal experiments and by clinical observations in patients who have suffered sympathetic denervation. Experimental studies, mainly in rabbits²¹ and cats,²² produced a short-term reduction of IOP following sympathectomy; long-term effects appear to have been variable or absent.

Cervical sympathectomy, by excision of the superior cervical ganglion, was used for the treatment of chronic simple glaucoma at the turn of the century.^{23,24} Swegmark²⁵ studied aqueous dynamics in patients with unilateral Horner's syndrome and concluded that sympathetic denervation reduced aqueous production and thus IOP in the ipsilateral eye. Wentworth and Brubaker²⁶ found a statistically

significant reduction of IOP in 21 patients with third nerve Horner's syndrome.

Because of the rarity of the clinical reports associating Horner's syndrome and glaucoma in the same eye, it is difficult to speculate on their relation. However, Julien and Vincendeau⁹ reported a case of FHC complicated by glaucoma that showed homolateral sympathetic injury after high dosage of amphetamine ingestion. Weinstein and Laugham²⁷ described a patient with congenital Horner's syndrome in whom bilateral open glaucoma was detected at the age of 57 years. Brazier²⁸ reported a case of bilateral cervical sympathectomy associated with unilateral Horner's syndrome in which the IOP was normal in the eye with Horner's syndrome, but ocular hypertension (in the presence of normal visual field and optic disc) was disclosed in the contralateral eye. The author suggested that the normal IOP in the eye with Horner's syndrome, and the normal visual field and optic disc in the fellow eye, might be due to some antiglaucomatous 'protective' mechanism produced by the sympathetic denervation. In view of the hypotensive effects of sympathetic lesions on ocular dynamics^{23,26} one is surprised that, in cases with FHC, the associated Horner's syndrome in the ipsilateral eye had no prophylactic, or at least, alleviating influence on the complicating glaucoma.

In the cases described here the mechanism of the interaction between Horner's syndrome and glaucoma may have several possible causes. First, the occurrence of these two conditions was entirely independent and simply coincidental. A second possibility might be that Horner's syndrome is, if not responsible for the glaucoma, then at least an aggravating factor. This is unlikely, because there is no clinical or experimental evidence that the IOP can rise as a result of ocular sympathetic denervation in humans. A third possibility is that Horner's syndrome preceded the development of the cyclitis and glaucoma by many years and might have been associated with normal or hypotensive IOP before and in the first stages of the FHC; later, with the aggravation of cyclitis, the augmented protein levels in the anterior chamber produced inflammatory damage to the trabeculum, overcoming the eventual ocular hypotensive effect of Horner's syndrome. This possibility seems to be the most satisfactory explanation.

A long follow-up of patients with FHC and Horner's syndrome illustrates the therapeutic difficulties encountered when this peculiar combination is complicated by glaucoma. The reason for the complete resistance of ocular hypertension to medical and surgical therapy in such cases is not clear.

Additional studies are necessary to evaluate the

incidence of sympathetic nervous damage in patients with FHC and to perceive its effect on the outcome of the glaucoma.

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Significance of intraocular lens power calculation

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SUMMARY A total of 94 patients underwent extracapsular cataract extraction and insertion of Sinsky style two-loop posterior chamber intraocular lenses. Forty-six eyes received a standard power IOL and 48 eyes were given a preoperatively calculated IOL. A significant difference was found in the two groups with regard to the postoperative refractive error and uncorrected visual acuity.

Posterior chamber intraocular lens (IOL) implantation is rapidly becoming the preferred method of visual rehabilitation after cataract surgery. Patients opting for intraocular lenses nowadays demand the best optical correction. To achieve ideal and optimum results, estimation of correct IOL power is necessary. The precision of such calculations depends mostly on the accuracy of ultrasonic bio-

metry as well as corneal curvature measurements.

With the increasing availability of lens implants in the third world, a great majority of patients will have their aphakia corrected by intraocular lenses in the near future. A-scan biometry is unlikely to be within the reach of many practising ophthalmologists in these countries. Very few studies have compared the outcome of implanting a standard powered and an individually tailored posterior chamber IOL.¹ We report such a study with a view to assessing the significance of calculating the IOL power preoperatively.

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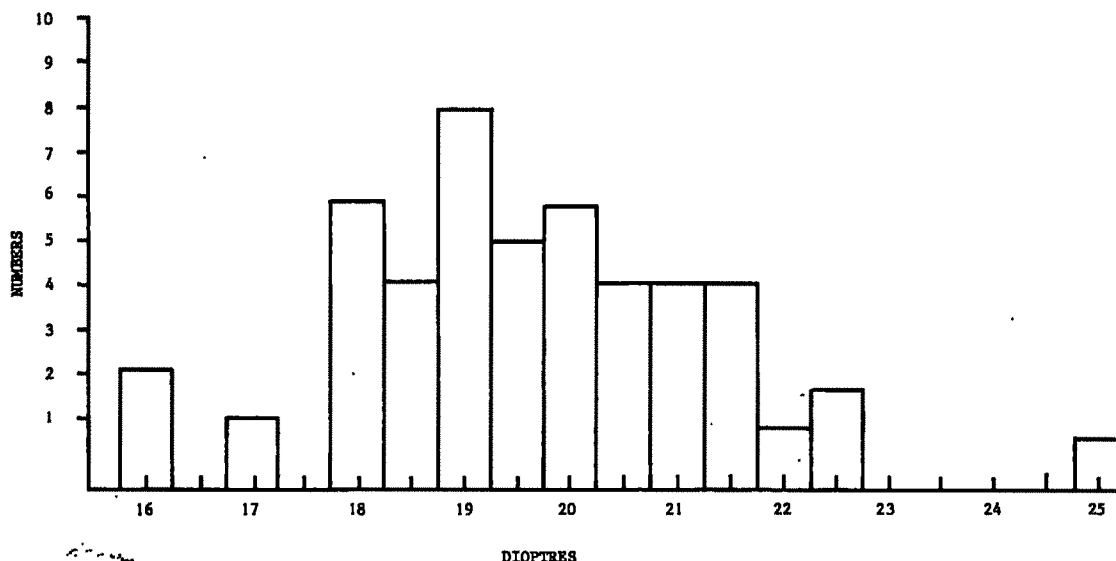


Fig. 1 Range of intraocular lenses used in the measured group.

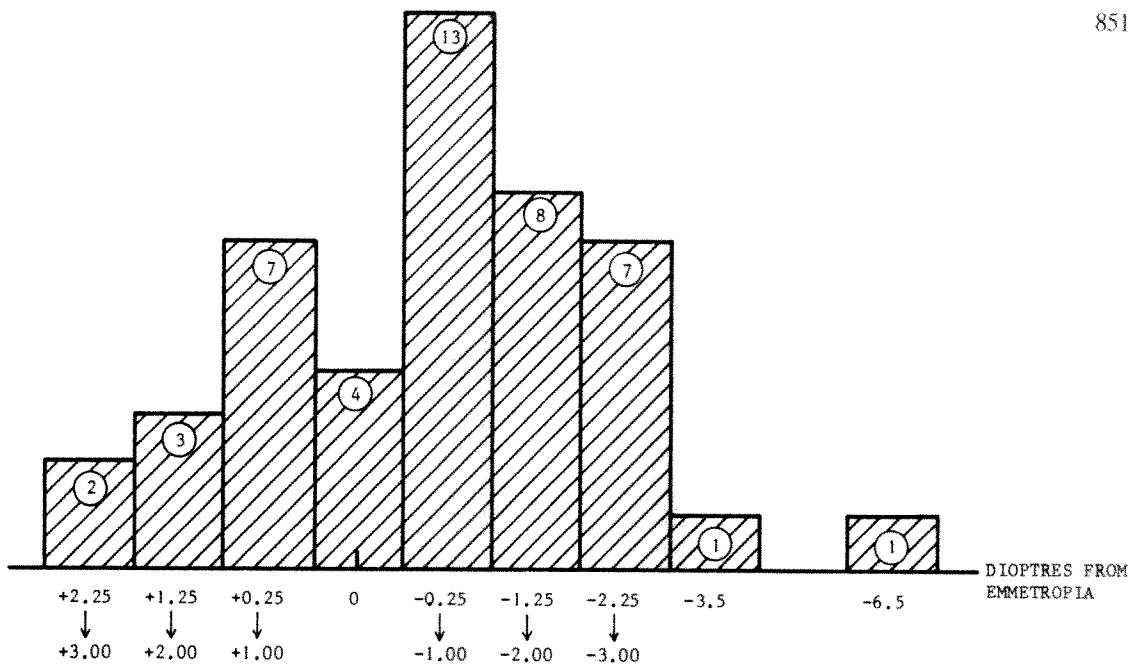


Fig. 2 Difference between the postoperative spherical equivalent refraction and emmetropia. Unmeasured group $n=46$.

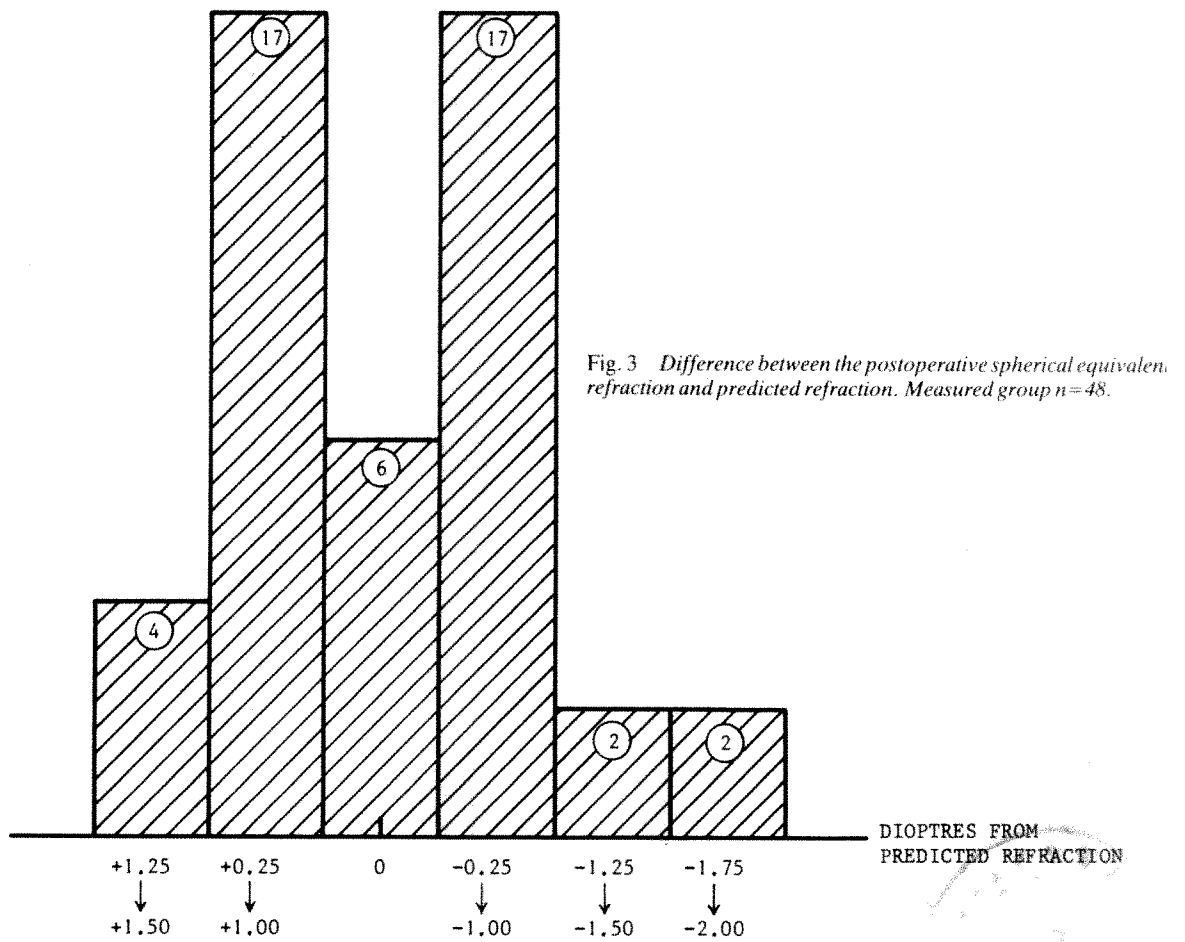


Fig. 3 Difference between the postoperative spherical equivalent refraction and predicted refraction. Measured group $n=48$.

Material and methods

Ninety-four patients were operated upon under general anaesthesia and with a Zeiss operating microscope. A standard extracapsular cataract extraction was performed by using the McIntyre manual aspiration system. A Sinsky style two-loop posterior chamber IOL was inserted by the same surgeon (MS). No viscoelastic material was used in this series. The limbal wound was closed with six to seven 10/0 monofilament sutures.

The first group of consecutive 46 patients received a standard power IOL of 19.5 dioptres, ± 0.5 dioptre, depending on availability. The second group of consecutive 48 patients had their IOL power estimated preoperatively. Axial length measurements were done with Cooper Vision Ultrascan digital A, which uses an applanation transducer. The corneal curvature was measured with a Bausch and Lomb keratometer. The IOL power required to produce 1 dioptre myopia was calculated by computing the SRK formula.²³

All patients were refracted between 8 and twelve weeks after surgery. The postoperative residual spherical equivalent refraction was determined for every pseudophakic eye. Patients having postsurgical astigmatism greater than 2 dioptres were not considered for the study.

Results

The 'unmeasured' group consisted of 46 patients. Their ages varied between 28 and 77 years, mean 57.8 years. The 'measured' group consisted of 48 cases. Their ages ranged from 35 to 80 years, mean 59.3 years. The intraocular lenses implanted in the measured group ranged from 16 to 25 dioptres (Fig. 1).

The postoperative visual acuity is shown in Table 1. The postoperative corrected visual acuity was similar in the two groups. However, there was a significant difference in the uncorrected postoperative visual acuity in the two groups ($p < 0.5$). 58.3% of the patients in the measured group could see 6/12 or better uncorrected as compared with only 32.6% in the unmeasured group. Only 12.5% of cases in the measured group had uncorrected vision below 6/18, whereas 43.5% of patients in the unmeasured group had vision worse than 6/18.

Fig. 2 shows the distribution of the difference between the spherical equivalent refraction and emmetropia for the unmeasured group. 52% of the patients fell within 1 D of emmetropia, 95.6% within 3 D. There were two patients outside this range measuring -3.5 D and -6.5 D postoperative residual pseudophakic refractive error.

Table 1 Postoperative visual acuity

Vision	Uncorrected		Corrected
	Measured group	Unmeasured group	Measured group
6/5	1	0	10
6/6	4	2	23
6/9	8	5	12
6/12	15	8	3
6/18	14	11	0
6/24	4	3	0
6/36	2	9	0
6/60	0	8	0

Fig. 3 shows the distribution of between the spherical equivalent predicted refraction for the measured group 83.3% of the cases fell within predicted refraction and 100% with eyes in this group showed postoperative within 2 D of myopia (Fig. 4). 87.5% within 1 D of the expected refraction.

Discussion

Calculation of IOL power preoperatively to achieve a desired refraction and a high ametropia.⁴ It has been shown even for planned ametropia in the accuracy of IOL power estimation similar to that found in previously.¹ Our study has shown that patients calculated IOLs achieved a much better visual acuity than those in the unmeasured group though there was little difference in visual acuity in both groups. Unexpected error was not present in the measured group whereas two such cases were encountered in the unmeasured group. Similar observations have been reported by other workers.^{4,24} Our data suggest that the margin of refractive error can be reduced by preoperative determination of IOL power.

Ultrasonic lens power estimation is a technique used by every implant surgeon in the developed world. Insertion of a standard power lens without the use of the residual pseudophakic refraction by means of a contact lens or spectacles is the only method to practise. Intraocular lens power is determined clinically if the surgeon knows the patient's basic refraction. Binkhorst²⁵ has listed possible sources of error in the clinic of lens power. It is extremely difficult to obtain the basic refraction in an Asian population. However, reason

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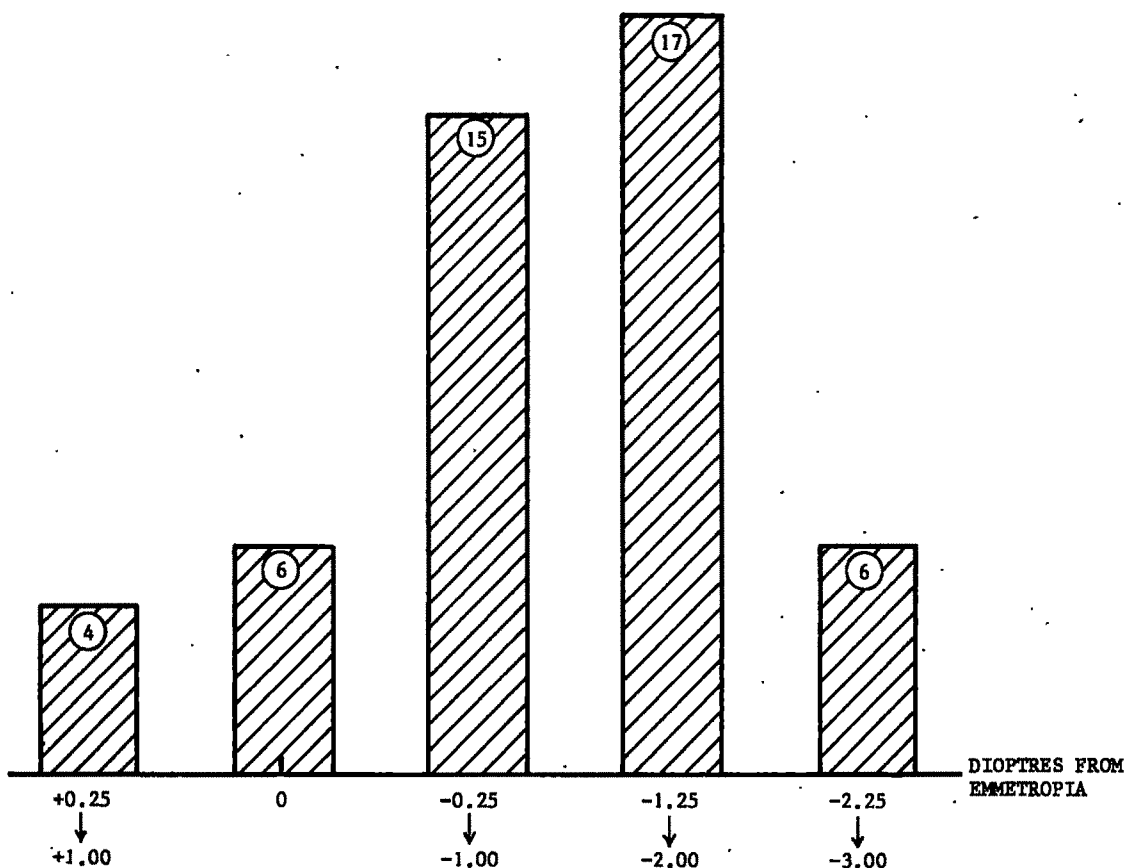


Fig. 4 Difference between the postoperative spherical equivalent refraction and emmetropia. Measured group $n=48$.

have been reported by implanting a standard power IOL.¹⁶ In our measured group the majority (68%) of the lenses inserted ranged from 18 to 20.5 dioptres. An appropriate range of lenses most suitable for the local population can be reasonably determined by conducting a pilot study using preoperative ultrasonography coupled with the knowledge of post-operative residual pseudophakic refractive error. Hence the routine use of lens calculation may be dispensed with if the resources to carry it out are limited. A careful selection of patients might reduce unexpected surprises but will not eliminate them, and both the patient as well as the surgeon should be prepared to face them.

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Chemical burns of the eye: causes and management

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SUMMARY For the 14 months 1 January 1985 to 28 February 1986 all cases of chemical eye injury presenting to the Croydon Eye Unit were analysed. Of the 180 cases 19 were caused by assaults and 14 were admitted for treatment. The wide range of injurious substances is emphasised, and the circumstances of injury are listed. A discussion of the management of chemical eye injury is included.

Chemical injuries of the eye form a small but significant fraction of ocular trauma. Three recent studies¹⁻³ put the incidence at 7, 8.7, and 9.9% of all ocular trauma, respectively. While many of these injuries are trivial, with no lasting adverse effects, others, notably those involving strong alkalis and to a less extent acids and other noxious substances, are potentially blinding. This study was prompted by a recent rise in the incidence of chemical trauma due to assault seen at Croydon Eye Unit, and set out to determine what substances are involved, which people are at risk, and the frequency of assault cases.

Patients and methods

The Croydon Eye Unit serves a largely residential area, population 300 000, with total attendances 33 000 and new attendances 11 000 per annum, based on 1984 figures.

Data were extracted from the case histories of all 180 cases of chemical eye injury presenting during the study period.

Results

Of 180 cases 136 were male and 44 female. Forty-one patients (23%) suffered bilateral injuries. The age distribution (Fig. 1) shows a marked preponderance of people of young working age, especially ages 16 to 25.

The range of implicated substances (Table 1) is very large, there being at least 33 and probably many more chemical compounds. Three categories, alkalis (26%), acids (14%), and solvent based products (13%), together accounted for over half the cases.

Nineteen cases (10.6%) were the result of assaults. The injurious agent was ammonia in nine (possibly 10) and an antipersonnel gas in nine. Two of the assaulted persons had other injuries: both had cuts and bruises and one a fractured mandible. Circumstances and apparent motives for the assaults are detailed in Table 2.

One hundred and sixty-one cases (89.4%) were the result of accidents. Some details of the history were lacking in 28; of the remainder 84 (63%) had occurred at work, 44 (33%) at home, 4 (3%) at school, and one in a public house. In one case deliberate self injury was suspected. The occupations of those injured at work are listed in Table 3.

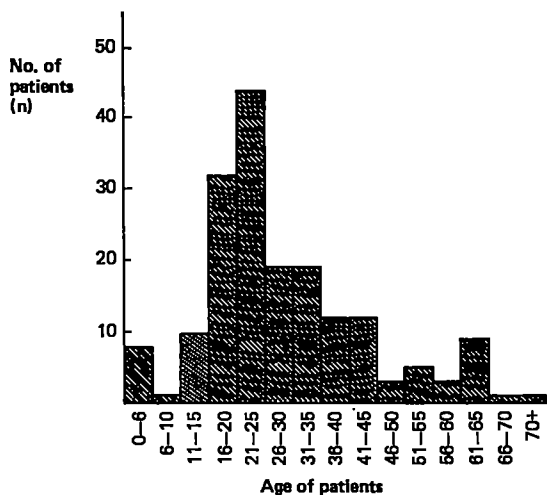


Fig. 1 Age distribution in 178 cases of chemical eye injury (age not recorded in two patients).

Table 1 *Injurious agent in 180 cases of chemical eye injury*

Agent	Number	Subgroups	No
Alkalis	47	Plaster	14
		Ammonia	10
		Oven cleaner/NaOH	8
		Wet cement	8
		Dry cement	6
		Truck wash*	1
Acids	25	Car battery	15
		Miscellaneous	8
		Gastric aspirate	1
		Boron trifluoride	1
Solvents/paints	24		
Detergents	15		
Antipersonnel sprays	9		
Adhesives	9		
Bleach	7		
Aerosols	6		
Surgical scrub	5		
Creosote	5		
Antifreeze	3		
Brake fluid	3		
Petrol	3		
Perfumes	3		
Copper sulphate	2		
Disinfectants	2		
Topical drugs	2		
Chilli Powder	1		
Contact lens cleaner	1		
Dispel (air freshener)	1		
Fire lighter fluid	1		
Gas canister	1†		
Insecticide	1		
Methyl diphenyl isocyanate	1		
Mouthwash	1		
Phenytoin solution	1		
Tattooing fluid	1		

*See text.

†Exact nature unclear.

ADMITTED CASES

Fourteen cases (six assaults and eight accidents) were admitted for treatment. All were males and their ages ranged from 14 to 53. Eight were bilateral cases. Indications for admission were (1) severity of the injury, (2) presence of severe pain and blepharospasm, or (3) presence of other injuries.

All six assault cases were caused by ammonia; the other implicated substances were cement (4), and plaster, brake fluid, truck wash (a detergent/alkali mixture), and a gas canister (type unknown) one case each.

Corneal injury ranged from severe punctate keratopathy to 95% epithelial loss. In the two most severely injured eyes there were persistent stromal scars, albeit with normal visual acuity.

Conjunctival injury consisted of patchy or confluent areas of epithelial loss, with small ischaemic areas in a minority of cases and significant limbal ischaemia (up to 25%) in four. Persistent sub tarsal

Table 2 *Breakdown of circumstances of 19 cases of chemical burn sustained as a result of malicious attacks*

<i>Occupation of victim</i>	
Sales assistant	2
Security officer	1
Van driver	1
British Rail steward	1
Petrol attendant	1
Not at work when attacked	13
Total	19
<i>Place of attack</i>	
Street	10
Shop	2
Train in motion	1
Outside bank	1
Petrol station	1
Public house	1
Night club	1
Unclear	2
Total	19
<i>Motive for attack</i>	
Robbery	6
Street fight	3
Petty quarrel	3
None apparent	7
Total	19

Table 3 *Occupations of 84 patients who sustained chemical eye injuries at work*

Builders and labourers	18
Electricians	12
Engineers	9
Nurses	7
Cleaners	6
Machine operators	6
Hotel and catering	4
Plating and printing	4
Drivers	3
Painters	2
Plumbers	2
Storemen	2
Carpenter	1
Car valet	1
Computer operator	1
Fireman	1
Glazier	1
Manager	1
Physiotherapist	1
Receptionist	1
Student	1
Total	84

foreign bodies were found in six eyes. Minor lid burns were seen in three ammonia cases.

Treatment involved immediate and repeated lavage of the conjunctival sac with sterile saline until the pH approached neutral. Particles of foreign material were removed after double eversion of the lids. Topical steroids were given in all cases, and in 17 cases an intensive regimen (½ hourly to 2 hourly dexamethasone) was instituted. Topical vitamin C

was applied in two cases and oral given in one. Mydriatics, analgesia, and padding were used as required.

The duration of stay in hospital ranged from one to 11 days determined by corneal re-epithelialisation and degree of discomfort. The total duration of treatment ranged from two days to 3½ months, tailing off according to clinical resolution.

Six patients defaulted from follow-up, and five had no sequelae and were discharged. One patient followed up elsewhere developed suspected functional visual loss in his fellow eye. Two patients had persistent corneal opacities but with normal visual acuities; one of these also had scarring of the upper tarsal plate without symblepharon.

NON-ADMITTED CASES

Of these 166 cases 110 (66.3%) were seen once only, 44 (26.5%) were followed up for up to one week, 11 (6.6%) for up to two weeks and only one for more than two weeks. In 92 cases (55.4%) topical steroids were used, often as a single dose of ointment plus an eye pad. In no case was any permanent injury observed.

ASSAULT VERSUS ACCIDENTAL CASES

Assault cases were over six times as likely to be admitted as accidental (31.6% versus 4.97% respectively). Alkalis were involved in 52.6% of assault cases and 23.0% of accidental cases.

Discussion

This study indicates the range and severity of ocular chemical injuries which may be encountered in a district general hospital. It underlines the enormous variety of chemicals which may be implicated and the potentially serious nature of injuries due to assault. However, it also indicates the relative rarity of truly sight threatening injuries.

In the management of chemical injury, alkali burns continue to present the greatest therapeutic challenge, both in severity and in numbers. The property of alkalis which confers this significance is their ability to saponify cell membranes and rapidly penetrate the cornea,⁴ causing a rapid rise in anterior chamber pH,⁵ with resultant damage to iris, ciliary body, and lens. Vascular channels are also damaged (see below), leading to ischaemic injury. Acids in contrast fix and coagulate superficial tissues and fail to penetrate deeply into ocular structures.⁴

In comparison with American series^{3,6} the alkali burns reported in the present study are of only moderate severity. There were only four cases of significant limbal damage and no major visual loss in the affected eyes. The assessment of severity⁷

involves three factors: damage to the lids and adnexae, degree of limbal ischaemic necrosis (more than one-third affected equals severe), and the degree of acute corneal stromal opacification (not seen in the present study). The visual results of one of these series⁶ emphasise this difference: of 63 cases 40% had a final acuity of less than 6/60 and 18% of no light perception; only 29% achieved an acuity better than 6/12. Two thirds of the cases in this series were assault victims, but the association with violent crime, alcoholism, and revenge attacks on unfaithful spouses contrasts with the motives of theft, petty quarrels, and gratuitous attacks seen in the present study.

Apart from motive, another factor influencing the outcome might be the nature or concentration of the noxious agent used.

In the management of chemical eye injury, first aid is of paramount importance. Immediate and copious irrigation with bland sterile solutions and removal of all solid particles should always precede a full history and examination. Testing the pH of the conjunctival sac or washings should indicate the presence of alkali, and, if it is present, irrigation should be prolonged. This gradually leaches alkali out of the tissues, where it would otherwise persist and cause further damage long after the pH of the external eye has returned to normal.⁴

In the early clinical assessment of assault cases a most important differential diagnosis exists between ammonia and antipersonnel agents such as CS gas. The picture is often confused by the assumption by victims and witnesses that any pungent smelling substance thrown at the face is ammonia. The following observations from personal experience may be helpful.

Antipersonnel agents are usually carried in an aerosol. They produce an intense choking with salivation, lacrimation, coughing, and a hot tingling sensation of all exposed skin. There is marked blepharospasm and photophobia. However, ocular examination reveals only a mild erythema of the skin and mild non-specific conjunctival injection with chemosis and epiphora. There may be slight punctate staining; otherwise all epithelium is intact. Full recovery from all effects occurs within hours.

The favourite vehicle for ammonia in this author's experience is the 'Jif lemon'. It produces a concentrated jet which the assailant can aim with great accuracy. The smell is characteristic but there is little systemic upset. The eyelids and skin may show blistering and erythema similar to superficial thermal burns. In milder burns the ocular signs are of injection and chemosis of the conjunctiva and geographical corneal and conjunctival epithelial loss, usually, due to Bell's phenomenon, on the infero-

nasal aspect of the globe. These areas stain with fluorescein and rose Bengal, and there may be more extensive areas of punctate staining. In more severe burns the conjunctiva and episclera are blanched, and microscopic examination shows disruption of the blood column (cattle trucking) in the vessels. Extensive blanching produces a deceptively white eye, but the end result is ischaemic necrosis leading to conjunctival scarring, symblepharon, and a dry eye, and, where the limbus is involved, to persistent corneal ulceration, thinning, and early or late perforation. In the most severe cases there is corneal opacification, intense exudation into the anterior chamber with flare, cells, and even hypopyon, and cataract formation. There may be an acute pressure rise due to shrinkage of corneal collagen.⁸

In the treatment of the mildest alkali burns topical steroid/antibiotic ointment plus padding may be all that is required, but, in cases involving significant epithelial loss, steroids and mydriatics should be intensively applied. 10% potassium ascorbate, thought to act by scavenging free radicals released by degranulating polymorphs⁴ and to reverse a local alkali induced scorbutic state,⁹ can be given topically every one to two hours. Application is painful. Citric acid chemotactically inhibits polymorphs and reduces the incidence of corneal ulceration in experimental studies.¹⁰ The collagenase inhibitors L-cysteine and acetylcysteine have also been used. In extreme alkali burned eyes the former had some beneficial effect¹¹ while the latter did not.¹²

Persistent or recurrent corneal epithelial defects may be treated with therapeutic soft contact lenses, but care must be taken to ensure adequate tear volume and quality.³

In the longer term surgery on the lids, conjunctiva, and cornea may be required. In the worst cases a full thickness corneoscleral graft may be attempted, but the prognosis for the restoration of useful vision is often poor.

The alkali burns in this series all re-epithelialised well. The beneficial early effects of steroids in reducing the inflammatory reaction were evident, but the reported harmful later effects in promoting corneal melting and perforation by impairing the repair process³ were not seen.

This may again reflect the absence of really severe injuries from this series. It is unproved whether withholding steroids would in fact have led to significant visual loss, but in the absence of evidence to the con-

trary it would seem reasonable to encourage their intensive topical use in all but the most severe burns, at least for the first few days after injury.

In Croydon admissions due to chemical eye injury appear to be on the increase. In 1982 there were seven cases (five accidental), in 1983 one, in 1984 two, in 1985 12, and in the first six months of 1986 eight cases. The proportion due to assaults is also increasing, which presumably reflects the rise in all crime. Whether chemical injury as a whole is increasing is not clear, but this study shows that a large number of cases must be preventable by the provision and use of adequate eye protection at work. Men of young working age are clearly the most at-risk group, and may be the most resistant to the use of this kind of protection. While the majority of cases are likely to be minor, where significant injury has occurred early and correct management may secure a good prognosis and minimise long term sequelae.

My thanks to Mr P J Holmes Sellors, Mr M D O'Riordan, and Miss H C Seward for allowing me to report patients under their care.

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Retinoblastoma: report of a case with minimal retinal involvement but massive anterior segment spread

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SUMMARY The case is described of a unilateral retinoblastoma in a 7-year-old girl which was initially misdiagnosed because of massive anterior segment involvement in the apparent absence of a retinal lesion. Only on histopathological examination of the enucleated eye was the presence of retinal tumour established, this being confined to two minute foci at the extreme periphery.

Invasion of the anterior segment by retinoblastoma is a well recognised if not very common complication, and in that it may simulate ocular inflammation it is a significant source of misdiagnosis.^{1,2} Seeding from an endophytic tumour is the usual cause of such spread, but appreciation of the true nature of the disease process can be difficult if associated cataract formation or vitreous exudates interfere with examination of the posterior segment. Nevertheless, given a proper index of suspicion, recourse to alternative methods of investigation such as ultrasonography and CT scanning should lead to the correct diagnosis. More difficult is the much rarer diffuse infiltrating growth pattern,^{3,4} since the retina may appear clinically normal despite adequate visualisation.

In this report we describe a child with massive anterior segment invasion in which the retinal involvement was confined to two minute foci at the extreme periphery. The paucity of retinal involvement is unprecedented in our experience of over 1000 retinoblastoma cases and we know of only one other case in the literature to invite comparison.⁵

Case history

A 7-year-old girl presented in March 1985 complaining of redness and blurring of vision of her right eye for about four weeks. On examination visual acuity was reduced to 6/60. Slit-lamp biomicroscopy showed a severe anterior uveitis with large iris nodules (Fig. 1) and cells and opacities in the anterior vitreous. Investigations, all of which were negative, included a

full blood count, plasma viscosity, toxoplasma dye test, and conjunctival biopsy for sarcoidosis. A presumptive diagnosis of granulomatous uveitis was made, and treatment was begun with intensive topical corticosteroids and systemic prednisolone 5 mg three times a day. Subsequently the intraocular pressure became raised to 44 mmHg, and because it failed to respond to antiglaucoma therapy with timoptol 0.25% twice daily, propine 0.1% twice daily, and acetazolamide 125 mg four times a day a cyclocryotherapy operation was performed at the end of May 1985.

The intraocular inflammation remained extremely active despite an anterior sub-Tenon's capsule injection of methylprednisolone (Depomedrone). In early June 1985 a blood stained hypopyon developed (Fig. 2) and the lens became cataractous. At the end of June 1985 it was suspected that the eye might be

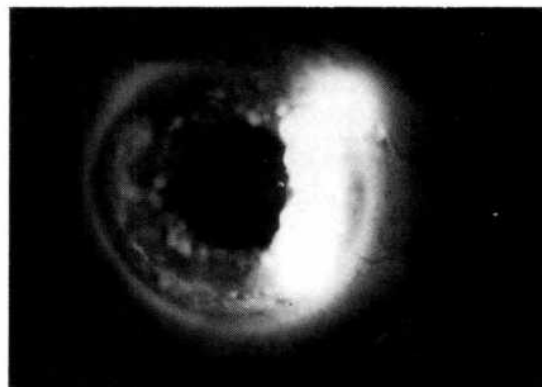


Fig. 1 Nodular infiltration of the iris by retinoblastoma.

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Fig. 2 Blood stained pseudohypopyon in conjunction with retinoblastoma and secondary cataract.

harbouring a malignant tumour, and diagnostic aspirates were taken from the aqueous humour and anterior vitreous. At the same time the iris was biopsied and the lens excised with a vitreous cutter through a pars plana incision. After the lens was removed a mass of white friable tissue was found in the area of the inferior pars plana. Following a preliminary histological report which suggested the presence of a malignant tumour an enucleation was performed two weeks later.

In February 1986 the prosthesis became tilted owing to an orbital swelling which quickly developed into an expanding orbital mass. In mid March 1986 an excision biopsy of the mass was performed and histology showed recurrence of the tumour. The patient was treated by orbital radiotherapy and adjuvant chemotherapy. Staging investigations prior to the institution of chemotherapy showed no

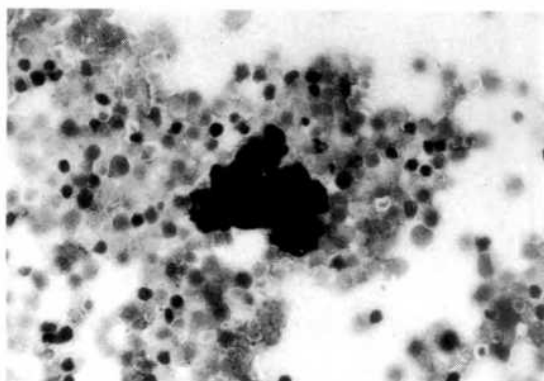


Fig. 3 Aqueous tap showing cells with small, darkly stained nuclei and scanty cytoplasm. Some cells are separate, others are in clumps and many are degenerate. Haematoxylin and eosin.

evidence of gross metastatic disease, but monoclonal antibodies on the bone marrow aspirate did show a few cells positive for neuroectodermal markers suggesting possible infiltration of her bone marrow with retinoblastoma cells which were not identifiable on standard light microscopy. Following completion of the initial course of chemotherapy the marrow aspirate was negative for cells of neuroectodermal origin on monoclonal antibody studies. Since then the patient has received two further courses of chemotherapy and is due to have more. In June 1986 she was alive and well, with no sign of further recurrence.

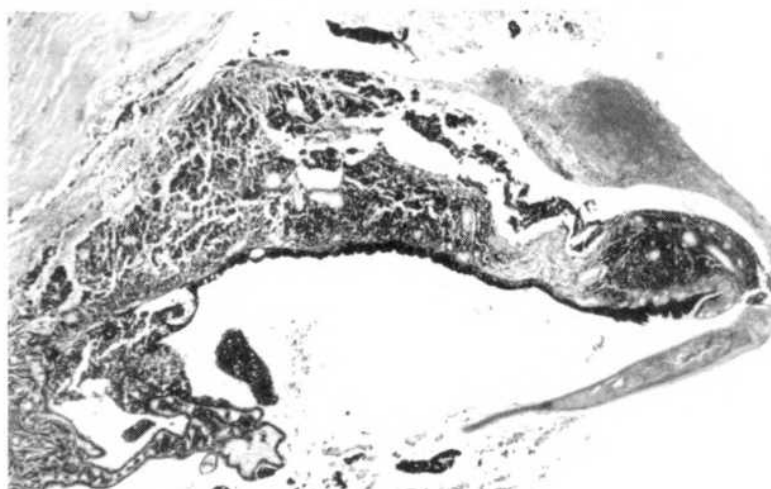
PATHOLOGY

Initial biopsies. A piece of iris removed at the time of lensectomy showed the stroma to be replaced almost completely by cells that were mostly round with quite strongly basophilic nuclei and hardly any cytoplasm. Some nuclear pyknosis and karyorrhexis were also seen. Samples from the aqueous (Fig. 3) and vitreous humours contained similiar cells, lying both singly and in clumps, and some haemorrhage. Immunohistochemical staining by a peroxidase-antiperoxidase method gave negative responses for cell-bound immunoglobulin using a polyvalent anti-serum, for S-100 protein, and for γ -neuron-specific enolase. Despite the lack of confirmatory evidence from the marker studies of a neuronal derivation a tentative diagnosis of retinoblastoma was made.

Enucleation specimen. There was evidence of a recent superior iridectomy, and the residual iris had an uneven, nodular, and greyish white appearance. Opening the globe in a vertical plane and removing the nasal calotte revealed soft, creamy nodules covering much of the posterior surface of the iris and similar material overlying the ciliary body. A little haemorrhage was observed on the posterior retinal surface and in the anterior vitreous, but otherwise the retina showed no further abnormality on macroscopic examination.

Light microscopy showed that most of the iris stroma and much of the ciliary body was infiltrated and replaced by round cells comparable to those seen in the earlier biopsy (Fig. 4). In places, particularly within the ciliary body, there was a tendency for the cells to form cords or ribbons, but true Flexner-Wintersteiner rosettes were not seen (Fig. 5). There were numerous islands of similar cells within the posterior chamber and in the anterior chamber, where they also lined the back of the cornea and occluded the drainage angle. The cells at the centre of some of the larger clumps were necrotic. Sections passing through the site of surgical intervention showed tumour cells in proximity to the scleral incision, but there was no sign of extraocular tumour.

Fig. 4 Section of the enucleated eye showing massive infiltration of the iris by small, darkly stained tumour cells. Free lying tumour cells in the aqueous, some haemorrhage and a remnant of lens are also seen. Haematoxylin and eosin.



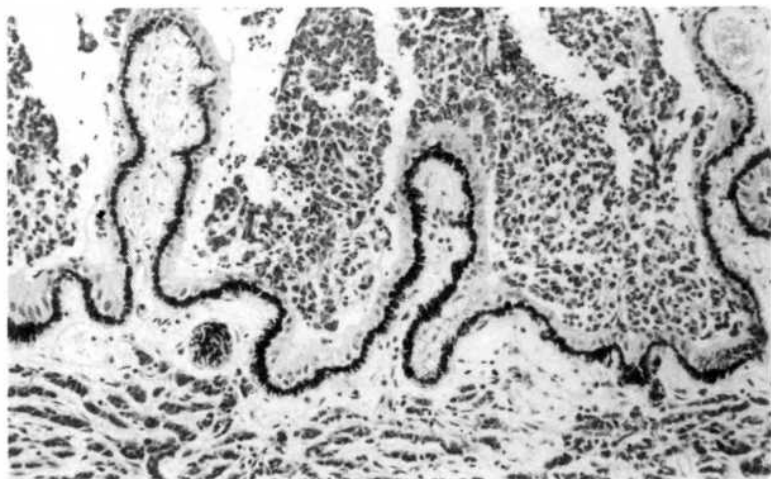
The lens capsule with some residual lens material was adherent to the pupillary margin of the iris, and there was blood in the anterior vitreous. Some atrophy of the corneal epithelium, possibly reflecting the effects of raised intraocular pressure, was also seen. Initial sections of the retina revealed no abnormality (Fig. 6) and it was only after examining multiple levels that two small, discrete foci of cellular proliferation comparable to that seen in the anterior segment were identified between the 11 and 12 o'clock meridians and the 6 and 7 o'clock meridians respectively at the extreme periphery (Figs. 7, 8). Neither focus was more than 1.5 mm in diameter, and there was minimal thickening of the affected retina. The inferior tumour proliferation was separated from the

pars plana ciliaris by about 1.0 mm of atrophic, acellular retina. Origin of the neoplastic process from the bipolar cell layer appeared possible. Away from the tumour the retina appeared to be normal, as did the optic nerve and choroid.

Immunohistochemistry on paraffin embedded tissue gave a variable but, in places, unmistakable staining response for γ -neuron-specific enolase. Reactions for S-100 protein and glial fibrillary acidic protein were negative.

Examination of formalin fixed, free lying cells recovered from the posterior chamber by transmission electron microscopy revealed occasional cilialike structures with a ring of nine doublet microtubular structures but no central component (9+0)

Fig. 5 Tumour cells in the ciliary body are forming cords, while those on its surface are randomly arranged with little evidence of rosette formation. Haematoxylin and eosin.



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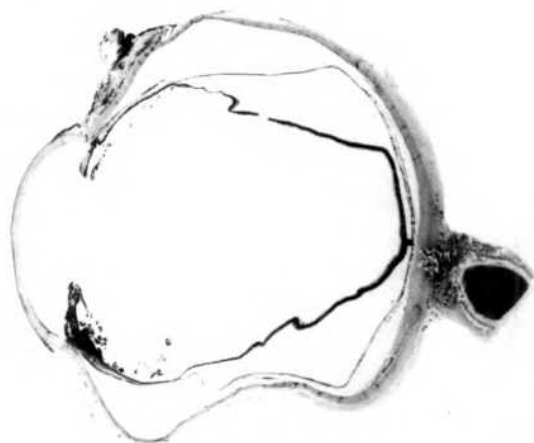


Fig. 6 Vertical section of the enucleated eye shows tumorous infiltration of the iris and ciliary body, particularly inferiorly, but the retina shows no abnormality apart from artefactual detachment. Tumour cells are seen in the posterior chamber and anterior vitreous. Haematoxylin and eosin.

(Fig. 9) and numerous intercellular junctions of intermediate type.

Discussion

The morphology of the cells at the initial biopsy, while consistent with retinoblastoma, was far from conclusive and warranted the consideration of alternative diagnosis. Given that the clinical diagnosis of uveitis made when the patient first presented was not substantiated by an appropriate response to anti-inflammatory drug therapy or the histological

character of the cellular infiltrate, the principal alternative was acute lymphocytic or monocytic leukaemia. This would have needed to be in an aleukaemic phase, since examination of the peripheral blood revealed no abnormality, but the absence of other symptoms and signs made leukaemic infiltration an unlikely diagnosis. Moreover, there was no evidence of cell bound immunoglobulin as might have been expected in the case of lymphocytic neoplasia. Nevertheless, the diagnosis of retinoblastoma was to some extent one of exclusion, and the finding of an apparently normal retina when the enucleated eye was opened in the laboratory provoked temporary misgivings, at least, on the part of the pathologist responsible for the biopsy evaluation. The subsequent demonstration of cilia-like structures with the 9+0 configuration characteristic of retinal photoreceptor cells and of many retinoblastomas^{6,7} served, however, to support the diagnosis, and the finding of intermediate junctions between the cells, while not conclusive evidence of retinoblastoma, excluded a leukaemic process.

The demonstration of neuron-specific enolase in some cells was also indicative of a neuronal tumour. In a study by Terenghi *et al.*⁸ all but one of 30 retinoblastomas stained for neuron-specific enolase, irrespective of the degree of differentiation, but other reports^{9,10} suggest that this enzyme is usually confined to the more primitive tumours such as pertained in the present case. The demonstration of S-100 protein is a less reliable marker of retinoblastoma, for, while Terenghi *et al.*⁸ found it to be present in all but five of the cases they examined, others have provided uniformly negative reports.⁹

Immunohistochemical staining for glial fibrillary acidic protein was negative in the present case, and,

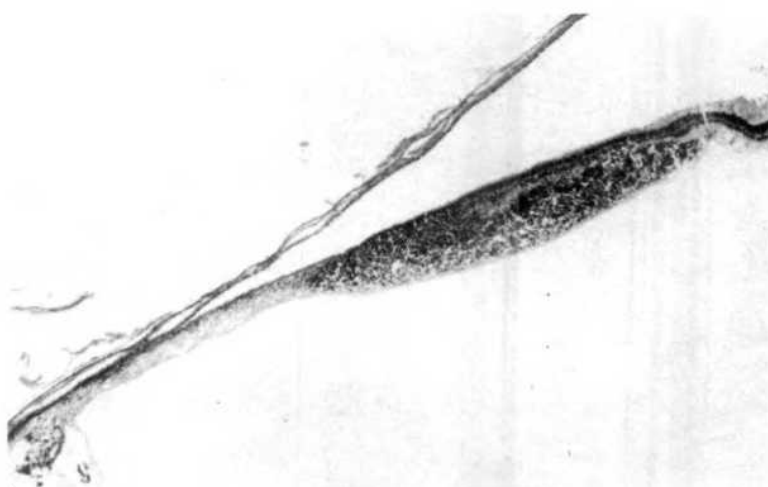


Fig. 7 The peripheral retina in the superior hemisphere shows a little focal increase in thickness due to the proliferation of retinoblastoma cells. Haematoxylin and eosin.

Fig. 8 A second small focus of tumour is seen at the inferior retinal periphery. Haematoxylin and eosin.



although a positive response has been described in respect of retinoblastoma cells maintained in tissue culture,^{10,11} others are agreed that the glial elements demonstrable in some tumours are not an integral part of the neoplastic process.^{8,12} Of the recognised

growth patterns of retinoblastoma the case under consideration compares most closely with the diffuse infiltrating type.^{3,4,13} Even so, two isolated foci measuring 1.5 mm at most, are only partially described by this designation, and the present case must

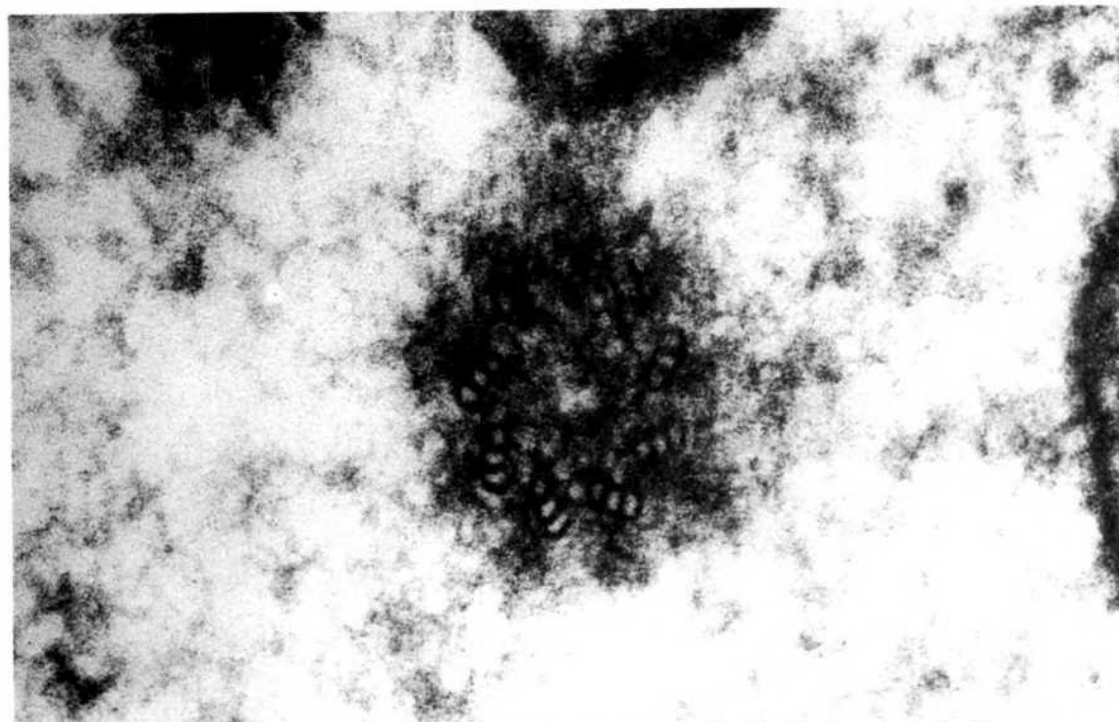


Fig. 9 Transmission electron micrograph of a tumour cell from the posterior chamber showing a 9+0 cilium-like structure. Uranyl acetate/lead citrate, $\times 200\,000$.

be regarded as an extreme rarity. The closest analogy in the literature appears to be the case presented by Reeser to the Verhoeff Society in 1975⁵ and depicted by Zimmerman,² but examination of the histological section indicates a slightly more extensive intra-retinal lesion than pertains in our case. They are, nevertheless, both likely to represent one end of a spectrum of the extent to which the retina can manifest the diffuse infiltrating form of retinoblastoma before presenting with predominantly anterior segment changes. It is noteworthy, although the relevance is obscure, that the age of the patient being reported was 7 years at initial presentation, that Reeser's case was 8 years old, and that seven of the 10 cases of diffuse infiltrating retinoblastoma described by Morgan³ ranged between 4¾ and 10 years in age. Morgan³ commented that retinoblastomas of the diffuse infiltrating type have a better prognosis than other types, but any prediction in the present case is clouded by recurrence of the tumour in the orbit eight months after enucleation.

We are grateful to Mr J D Griffiths, FRCS, who was responsible for the initial referral and for the enucleation, for permission to report this case, and to Dr A C E McCartney for electron microscopical data.

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Ocular malignant fibrous histiocytoma: clinical and histopathological characteristics

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SUMMARY A rare case of malignant fibrous histiocytoma involving the whole eye is reported in an Oriental 60-year-old man. Six months' follow-up after exenteration did not show any evidence of local recurrence or distant metastases.

Malignant fibrous histiocytoma was first described by O'Brien and Stout¹ in 1964. The orbit is a site of predilection of this tumour.² Litricin³ reported fibrous histiocytoma of the corneosclera in a 65-year-old woman, and Urdiales-Viedma *et al.*⁴ reported pleomorphic fibrous histiocytoma of the corneoscleral limbus in a 72-year-old woman. To our knowledge this is the first case of pleomorphic malignant fibrous histiocytoma involving the whole eye.

Case report

A 60-year-old man was examined on 9 July 1985 in the Department of Ophthalmology, JIPMER, Pondicherry, with the complaints of gradually increasing painless swelling under the left upper lid of one year's duration and progressive loss of vision for six months. Three months later there was gradual protrusion of the same eye, with severe pain and blood stained purulent discharge.

Examination of the left eye showed swollen lids and matted cilia. On retracting the upper lid there was a nodular swelling measuring 8.5×7 mm at the superior limbus. The whole of the bulbar conjunctiva was thickened, and the surface was irregular and firmly adherent to underlying sclera. Cornea, anterior chamber, iris, and lens were not identified. A nodular greyish mass was seen through the destroyed cornea (Fig. 1). On palpation the orbital margins were normal. The mass was tender and non-compressible. The preauricular and submandibular

lymph nodes were not enlarged. There was no perception of light. Examination of the right eye revealed immature senile cataract. The best corrected visual acuity was 6/12 (Snellen's chart). The intraocular pressure was 17.3 mmHg (Schiotz tonometer) and the fundus was normal. Systemic examination did not show any evidence of secondary growths.

A complete haemogram revealed no abnormality. X-rays of the orbits, optic foramina, and chest were normal. A clinical diagnosis of ocular tumour was made. Biopsy showed malignant tumour, but categorisation could not be made as the specimen was small. Exenteration of the left orbit was done on 28 August 1985.

HISTOPATHOLOGY

Macroscopic examination. The exenterated specimen of left orbit measured 31×29.2×28.7 mm.



Fig. 1 Swelling at the superior limbus. Greyish mass is seen through destroyed cornea.

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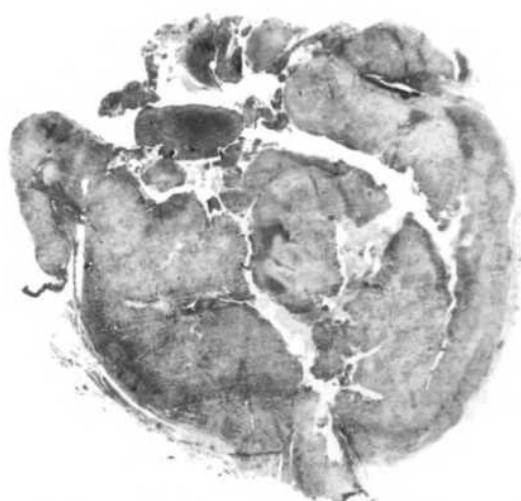


Fig. 2 Intraocular location of tumour with foci of necrosis. Tumour has come out of corneoscleral junction infiltrating the conjunctiva. Optic nerve also shows tumour infiltration. H and E.

There was an irregular nodular elevation under the upper eyelid measuring 8.5×7 mm. The cornea was completely ulcerated and was covered by necrotic tissue. The optic nerve measured 3 mm. Transillumination was negative in all directions. The eyeball was cut vertically. The cut section showed a lobulated greyish white tumour measuring 24.4×21.0×18.6 mm. The tumour was soft to firm in consistency, with foci of necrosis (Fig. 2). It occupied the whole eye, destroying the uveal tract and retina completely, and extended on to the optic disc. The lens was not seen. The sclera was infiltrated by the tumour just behind the equator on the inferior side and near the superior

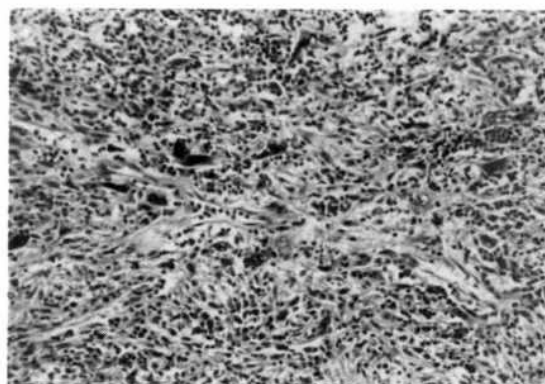


Fig. 3 Spindle shaped cells arranged in a storiform pattern. There are considerable number of giant cells and inflammatory cells. H and E.

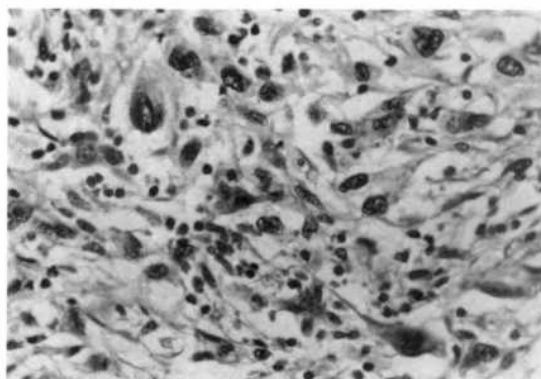


Fig. 4 Histiocyte-like cells. A fair number of inflammatory cells are also seen. H and E.

limbus. The nodule under the upper lid, on cut section, was continuous with the intraocular tumour at the limbus.

Microscopic examination. The tumour showed a variable histological pattern, having a storiform pattern in some areas and pleomorphic appearance in other areas. The tumour consisted of plump spindle cells in fascicles around inconspicuous vessels (Fig. 3). These cells had abundant eosinophilic cytoplasm with a round pale-staining central nucleus. In some areas there were plump cells with pronounced atypia mixed with a considerable number of histiocytes and other inflammatory cells (Fig. 4). The giant cells had multiple deeply staining nuclei and bright eosinophilic cytoplasm (Fig. 5). Typical and atypical mitotic figures were seen. Inflammatory cells, mainly plasma cells and lymphocytes, were conspicuous in some areas. Delicate collagen fibrils separated the tumour cells.

The tumour cells on staining showed faint positivity for neutral fat, but stains for glycogen were negative. Special stains failed to reveal cross

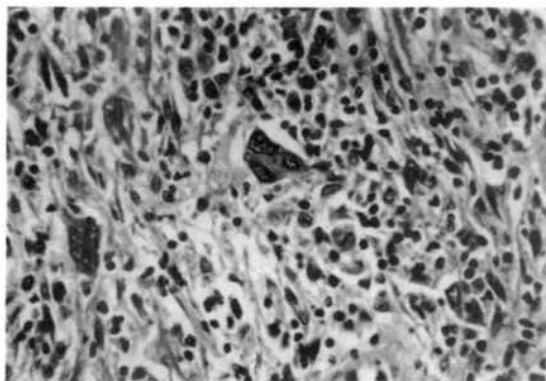


Fig. 5 Pleomorphic giant cells. H and E.

striations, ruling out a myogenic tumour. A diagnosis of malignant fibrous histiocytoma infiltrating the retina, uveal tract, conjunctiva, cornea, sclera, and optic disc was made.

Discussion

Malignant fibrous histiocytoma is a primitive mesenchymal tumour showing partial fibroblastic and histiocytic differentiation; it occurs commonly in late adult life.⁵ These tumours have a wide range of histological patterns—for example, myxoid, inflammatory, angiomatoid, with formation of bone and cartilage, pleomorphic, fibroblastic, xanthomatous, and xanthogranulomatous.⁴ Orientals (2%) are less commonly affected than Caucasians (91%) and Negroes (7%).⁵ These are seldom reported because of rare occurrence in the eye.^{4,6} Males and females are equally affected with orbital tumours,² though females are mainly subject to ocular tumours.^{3,4,7} The present case was in an Oriental 60-year-old man.

The sclera and corneal stroma are usually resistant barriers to the spread of tumour from episclera and conjunctiva.⁸ Litricin³ reported a case of fibrous histiocytoma of the corneosclera which invaded the iris, possibly following a perforation at the limbus during sclerokeratoplasty 11 months prior to enucleation. Delgado-Partida *et al.*⁶ reported a case of malignant fibroxanthoma in which the ciliary body was possibly invaded secondarily from the conjunctiva. In our case it is difficult to pinpoint the site of origin of the tumour. However, as the tumour is mainly intraocular in location, it seems more plausible to think that this tumour arose from retina and, after destroying the sclera and other structures, went

out at the superior limbus and presented as a nodule under the upper lid.

The prognosis of malignant fibrous histiocytoma depends on depth, size, and inflammatory component.⁵ Recurrences are frequent after local excisions.^{3,6} It is sometimes quite difficult on the basis of the histopathology to predict biological behaviour.² Death from local extension and distant metastases has been reported in malignant orbital tumours.² In the present case the history was of one year's duration and follow-up of six months after exenteration without local recurrence or distant metastases. The clinical course so far has been benign, though histologically the tumour is malignant. The same condition has been observed by Urdiales-Viedma *et al.*⁴

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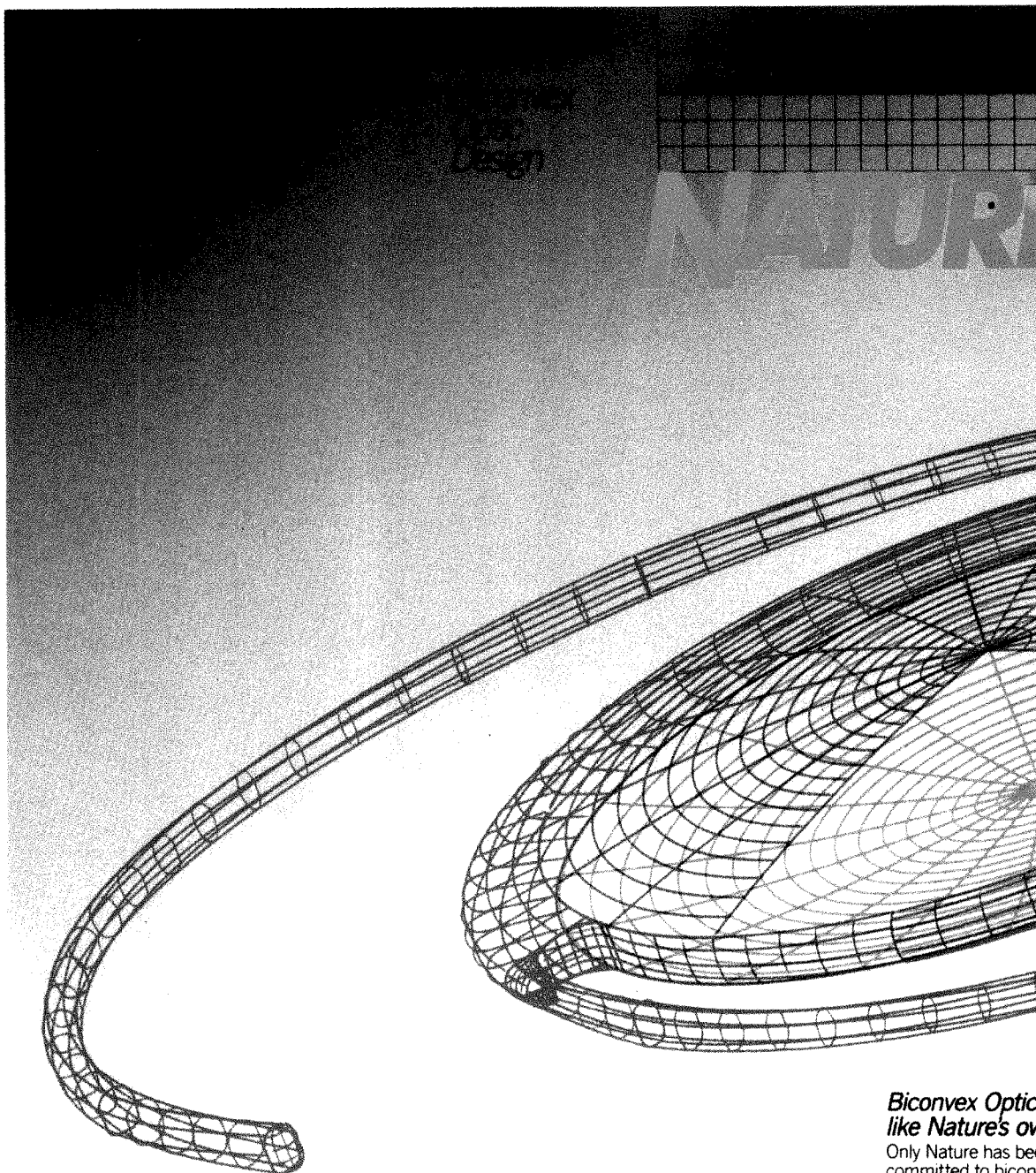
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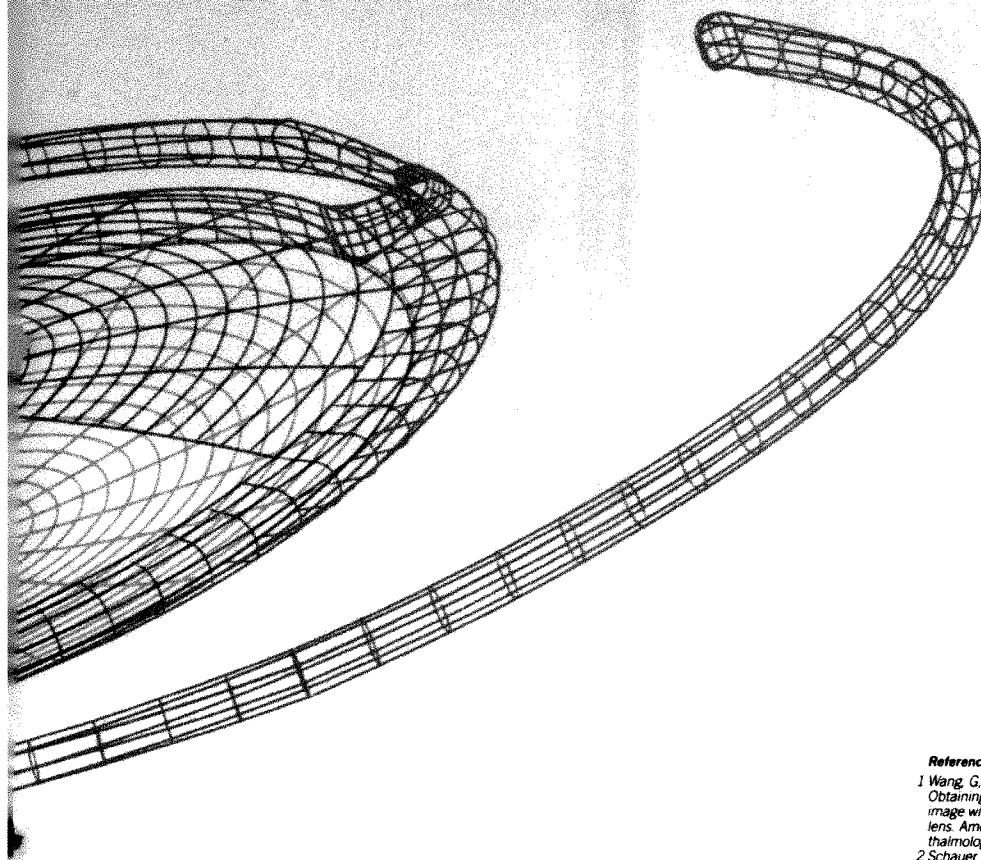
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Cytological and immunohistochemical study of the limbal form of vernal keratoconjunctivitis by the replica technique

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SUMMARY The cellular composition of the inflammatory infiltrate present in 13 patients with the limbal form of vernal keratoconjunctivitis was examined in the conjunctival scrapings and the limbic replicas by means of Giemsa stain and immunohistochemistry. Conjunctival scrapings showed the presence of mast cells, lymphocytes, plasma cells, polymorphonuclear leucocytes, and very few basophils in all the specimens. Eosinophils were present in only four scrapings. The superficial epithelium of the limbic lesion and the adjacent cornea and conjunctiva was studied by the replica technique. The limbic lesion area showed the presence of necrotic epithelial cells mixed with inflammatory cells, including eosinophils, mast cells, lymphocytes, plasma cells, and polymorphonuclear leucocytes and very few basophils. Most of the inflammatory cells were HLA-DR⁺. Many OKT₆⁺ cells were present, indicating the presence of Langerhans cells. T-lymphocytes including a few helper/inducer cells and many suppressor/cytotoxic cells, were detected in the infiltrate. In addition many B-lymphocytes were observed. These findings suggest that other immune mechanisms in addition to type 1 reaction are involved in the pathogenesis of the disease.

Vernal keratoconjunctivitis is a chronic, seasonally exacerbated bilateral external ocular inflammation. It is essentially a disease of childhood and youth, most frequently seen between the ages of 6 and 20. The disease is more common in males until after puberty, when the incidence in both sexes tends to be more equal.¹

There are three major forms of the disease: limbal, palpebral, and mixed. Coloured races are particularly prone to the limbal form of the disease,¹ and purely or predominantly limbal form of the disease appears to be found more frequently in black populations.^{2,3} Corneal findings are common and include punctate epithelial keratitis, epithelial macro-erosion, plaque formation, subepithelial scarring, and pseudogerontoxon.⁴

Vernal keratoconjunctivitis is usually considered

to be a type 1 hypersensitivity reaction mediated by IgE. This is suggested by the frequent presence of personal and family histories of atopy,⁵ by high IgE levels in serum and tears,⁶ by specific IgE antibodies to the pollen allergens in the tears,⁷ by elevated tear histamine levels,⁸ and by local and systemic eosinophilia.⁹

Locally produced pollen-specific IgG antibodies are detected in the tears of patients, suggesting that both IgE and IgG mediated immune mechanisms are involved in the pathogenesis of the disease.¹⁰ However, the mixed cellular infiltrate observed in the conjunctival tissues¹¹⁻¹³ suggests that other immune mechanisms may play a part in the pathogenesis of the disease. Delayed-type hypersensitivity of the cutaneous basophil type may play a part in vernal keratoconjunctivitis owing to the occurrence of basophils in the conjunctival tissue.¹¹ This hypothesis is also supported by the predominance of helper/inducer T-lymphocytes in the cellular infiltrate.¹⁴

The present study was undertaken to examine the

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cellular composition of the inflammatory infiltrate in the superficial epithelium of the limbic lesion and the adjacent cornea and conjunctiva in patients presenting with the limbal form of the disease. Monoclonal antibody staining techniques were employed to determine the involvement of T- and B-lymphocytes, Langerhans cells, and the expression of the major histocompatibility (MHC) class II antigens in material obtained by the replica technique.

Subjects and methods

SUBJECTS

Thirteen patients with the limbal form of vernal keratoconjunctivitis seen in the ophthalmic outpatient clinic of Mansoura University Hospital were included in the study. All the patients were examined by a slit-lamp. Cobalt blue filter and 2% sodium fluorescein solution were used to detect corneal ulcerations, and corneal and conjunctival changes were recorded.

The patients comprised eight males and five females. Their ages ranged from 4 years to 16 years, average 8.5 years. The symptoms given by the patients or their relatives were itching (13 patients), redness (eight patients), photophobia (six patients), lacrimation (three patients), and foreign body sensation (one patient).

The condition was bilateral in nine patients and unilateral in four. Circumcorneal disease was noted in all the patients, with encroachment on to the cornea in three patients (Fig. 1). The limbal lesion was greyish or pinkish and the bulbar conjunctiva near the cornea was injected. Trantas' dots were noted over the limbal lesion in two patients. Vernal keratopathy was noted in three patients. The first patient had an oval ulcer at the upper third of the

cornea with superficial stromal infiltration underneath, in addition to fine greyish punctate epithelial infiltrates distributed all over the cornea; the second patient had a whitish corneal plaque associated with epithelial opacification; the third patient showed punctate stains at the upper third of the cornea. Characteristic cobblestone papillae of the upper palpebral conjunctiva were noted only in the three patients with vernal keratopathy. The upper palpebral conjunctiva of another patient showed fine papillae. One patient with cobblestone papillae presented mechanical ptosis.

CONJUNCTIVAL SCRAPINGS

Conjunctival scrapings were taken from the upper palpebral conjunctiva under topical anaesthesia. The smears were air dried, fixed in absolute methyl alcohol for five minutes, and stained with Giemsa stain.

LIMBIC REPLICAS

Epithelium specimens from the limbic lesion and the surrounding cornea and conjunctiva were obtained by the replica technique.¹⁵ Replicas were obtained after drying the cornea and painting the lesion with a viscous solution of collodion in amyl acetate. After evaporation of the solvent the collodion membrane with the adhering superficial cells was peeled off. The replicas and the unstained flat mounts were examined by phase contrast and oblique illumination microscopy, and later subjected to immunohistochemical staining.

IMMUNOHISTOCHEMICAL STUDY OF THE REPLICAS

Ten replicas were stained by the following monoclonal antibodies: OKT₄-Leu3a, OKT₈, B₁, OKT₆, HLA-DR. The OK series of monoclonal antibodies were purchased from Ortho Pharmaceutical Co, Raritan, NJ, USA; Leu3a and HLA-DR were obtained from Becton-Dickinson, Sunnyvale, CA, USA; B₁ was obtained from Coulter Electronic, Hialeah, FL, USA.

OKT₄ and Leu3a define the helper/inducer T-cell subset^{16,17} and were applied simultaneously,¹⁸ OKT₈ defines the suppressor/cytotoxic T-cell subset,¹⁹ HLA-DR is directed against major histocompatibility (MHC) class II antigens.²⁰ B₁ reacts with all mature B-cells,²¹ and OKT₆ defines cortical thymocytes, epidermal Langerhans cells, and interdigitating reticular cells.^{22,23}

An indirect immunoperoxidase procedure was performed.²⁴ Following incubation with peroxidase-conjugated rabbit antimouse Ig (Dakopatts a/s, Copenhagen, Denmark), the reaction product was developed with 3-amino-9-ethylcarbazole (Aldrich



Fig. 1 Limbal form of vernal keratoconjunctivitis. Note the presence of circumcorneal disease with encroachment on to the cornea.

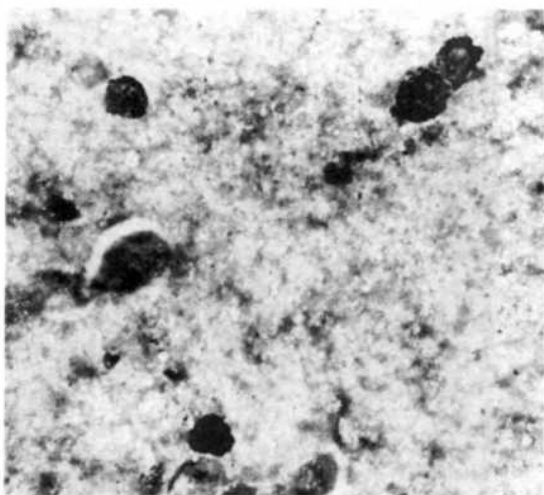


Fig. 2 Conjunctival scraping showing mast cells recognised by the presence of granules. Giemsa, $\times 470$.

Co Beerse, Belgium) and H_2O_2 .²⁵ The cells were briefly counterstained with Mayer's haemalum. Subsequently the cells were stained with Giemsa stain and examined by light microscopy.

Results

CONJUNCTIVAL SCRAPINGS

All the specimens contained sufficient number of cells. Many mast cells (Fig. 2), lymphocytes, plasma cells, and polymorphonuclear leucocytes were present in all the specimens. Occasionally very few basophils were seen. Eosinophils were present in only four specimens.

CYTOLOGICAL OBSERVATIONS OF THE REPLICAS

The replicas obtained from all the patients contained the lesion area and the surrounding corneal and conjunctival epithelium. Phase contrast and oblique illumination microscopy of the replicas allowed us to study the shape and arrangement of the superficial epithelium. In the lesion area the epithelial cells were necrosed and were of irregular shape and arrangement. In the punctate lesions seen clinically localised patches formed of necrotic epithelial cells were observed (Fig. 3). Outside the lesion area most of the epithelial cells were intact. Only some were swollen, rounded, and occasionally fused.

Giemsa staining showed that the epithelial cells in the lesion area were necrotic. They had dark swollen nuclei with little or no cytoplasm. Dense collections

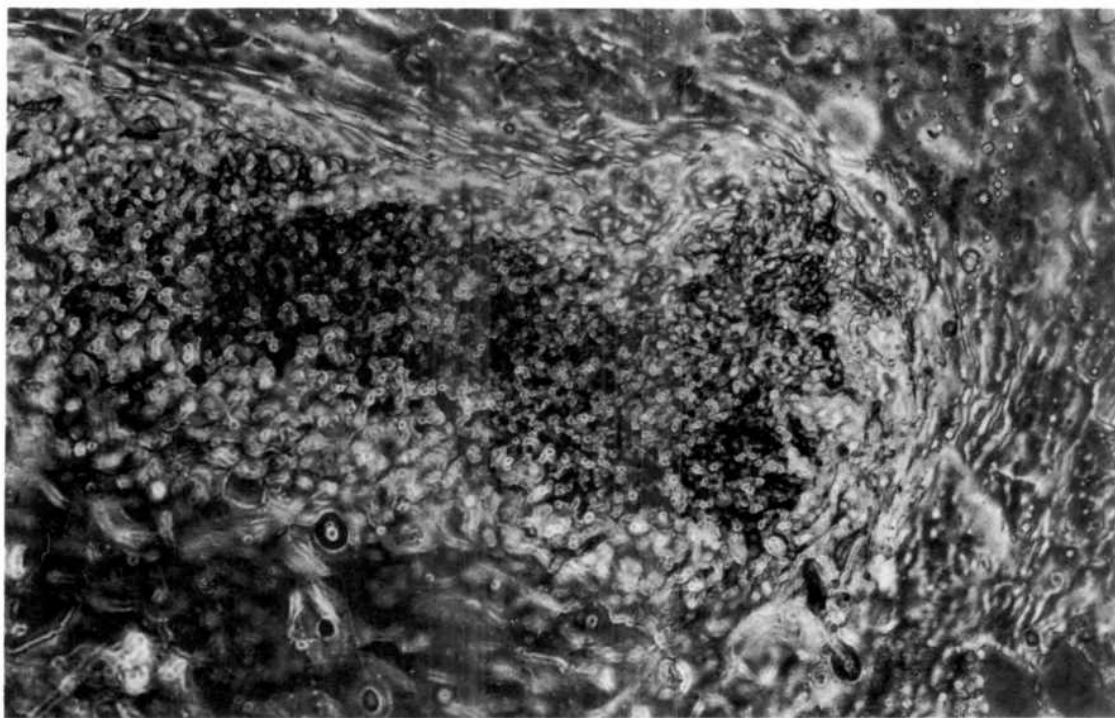
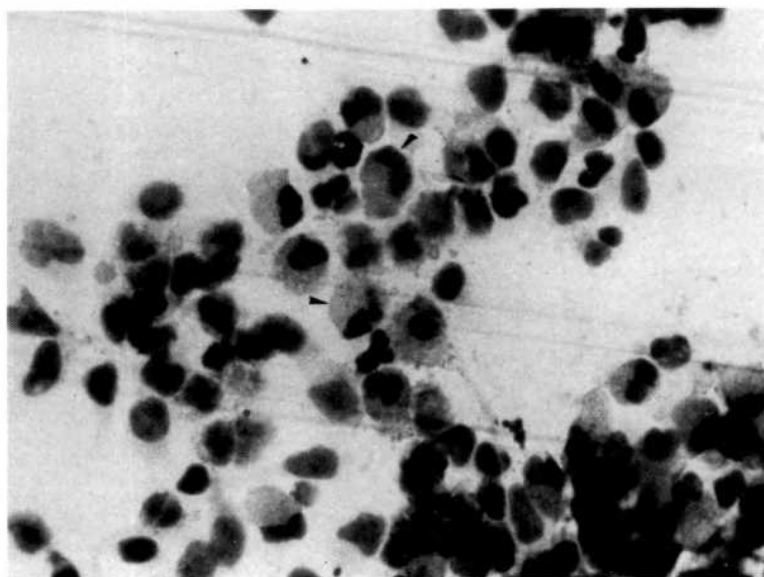


Fig. 3 Replica from a patient having vernal keratopathy. Note the presence of localised area of cell necrosis and degeneration representing a punctate clinical lesion. Phase contrast microscopy, $\times 175$.

Fig. 4 Replica showing necrotic epithelial cells mixed with inflammatory cells. Note the presence of many eosinophils (arrows). Giemsa, $\times 590$.



of inflammatory cells were present in the lesion area. In all cases the cellular infiltrate was composed of eosinophils which were either intact or fragmented with scattered eosinophilic granules, mast cells, lymphocytes, plasma cells, and polymorphonuclear leucocytes (Fig. 4). Basophils were occasionally seen. The surrounding epithelial cells showed granular cytoplasm. Some had swollen nuclei and others had small dark nuclei. Few inflammatory cells were seen scattered between these cells.

IMMUNOHISTOCHEMICAL RESULTS

Positive results were obtained in all the specimens examined. The epithelial cells in the limbic lesion area, as well as in the surrounding epithelium, were non-reactive for all the monoclonal antibodies used. The surface epithelium of the limbic lesion and the adjacent cornea and conjunctiva showed the presence of various types of inflammatory cells. These cells were present mainly in the area of the lesion, with few cells scattered in the surrounding epithelium. Most of the inflammatory cells expressed the major histocompatibility (MHC) class II antigens. T-lymphocytes including few $\text{OKT}_4\text{-Leu3a}^+$ (helper/inducer) cells and many OKT_8^+ (suppressor/cytotoxic) cells were present. B_1^+ cells were present in large numbers (Fig. 5). The presence of many OKT_6^+ cells indicated the presence of accessory cells (Langerhans cells).

Discussion

The presence of eosinophils and free eosinophilic

granules has been considered to be the most characteristic feature of the conjunctival scrapings in vernal disease.²⁶ Kimura and Thygeson²⁷ noted a characteristic fragmentation of the eosinophils in the conjunctival scrapings of patients with vernal conjunctivitis. We detected eosinophils in only four scrapings out of the 13 examined. Similar finding was noted by Abelson *et al.*,²⁸ who found eosinophils in the conjunctival scrapings of 63% of their patients with vernal conjunctivitis. They concluded that eosinophils present in deep and superficial conjunctival tissues as seen in biopsy specimens may not be recovered in scrapings; their absence from scrapings should not exclude the diagnosis of allergic ocular disease.

Numerous mast cells were present in the conjunctival scrapings of all the patients. On the other hand very few basophils were occasionally seen, indicating that mast cells are predominant in the conjunctival scrapings of our patients. In addition the scrapings showed lymphocytes, plasma cells, and polymorphonuclear leucocytes.

Epithelial invasion by mast cells, eosinophils, and basophils has been reported in vernal conjunctivitis.¹² Polymorphs¹³ and lymphocytes¹¹ were also noted.

The replica technique allowed us to study the superficial epithelium and the distribution of inflammatory cells in the limbic lesion and the adjacent corneal and conjunctival epithelium. In the limbic lesion area the epithelial cells were necrosed and lost their normal hexagonal shape and arrangement. They were mixed with dense collections of inflammatory cells. Outside the lesion area the epithelial cells

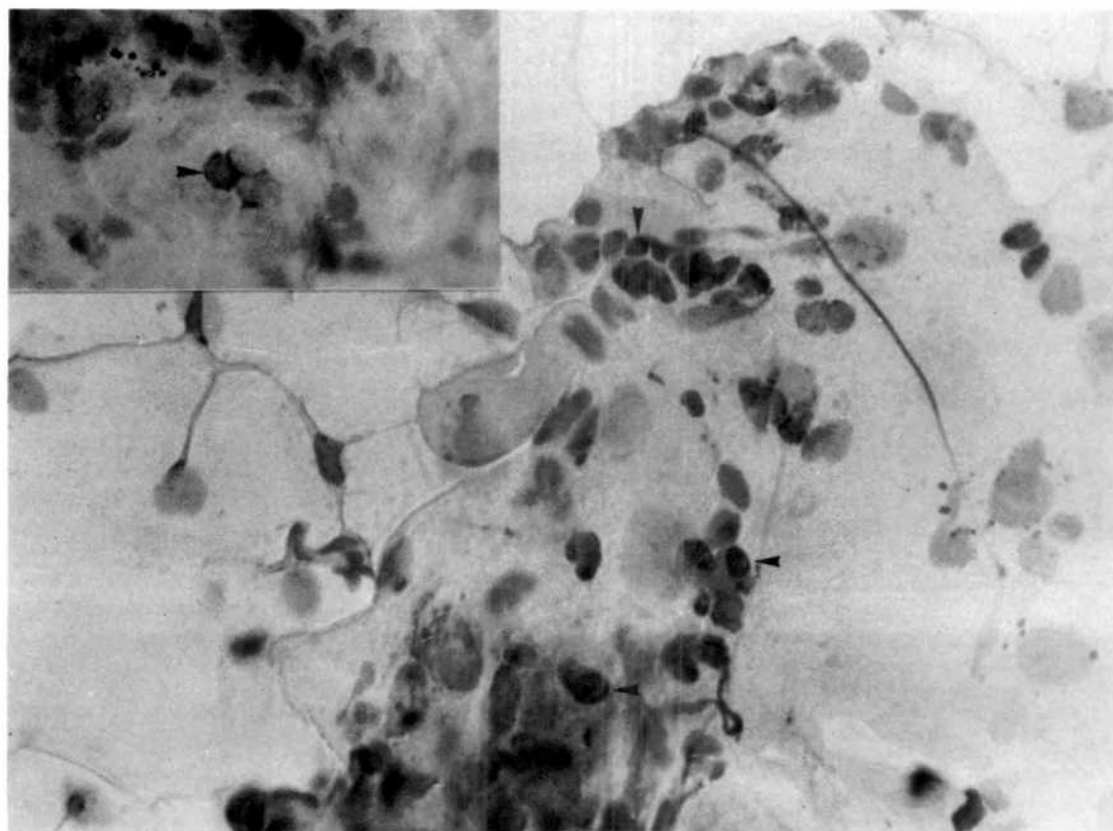


Fig. 5 Limbic replica showing the presence of B_1^+ B-lymphocytes (arrows). As shown in the insertion the positive reaction is a membranous staining. Immunoperoxidase, $\times 778$.

were more or less of normal shape and arrangement, but some of them were swollen, rounded, and occasionally fused. Few inflammatory cells were seen scattered outside the lesion area. The inflammatory infiltrate in the limbic lesion was composed of many eosinophils which were either intact or fragmented with the release of their granules, mast cells, lymphocytes, plasma cells, and polymorphonuclear leucocytes. As we observed in the conjunctival scrapings, basophils were very few and mast cells were predominant. Eosinophils were noted in all the limbic specimens obtained by the replica technique in spite of their presence in only four conjunctival scrapings. This indicates that examining the limbic lesion by the replica technique was more valuable than examining conjunctival scrapings in investigating this disease.

Immunohistochemical staining showed that most of the inflammatory cells present in the lesion area expressed major histocompatibility (MHC) class II antigens, indicating that they are immunologically active. We noted that many B-lymphocytes were present in the cellular infiltrate. This observation can

explain the findings of other authors who noted elevated levels of IgE in the tears of patients with vernal keratoconjunctivitis. T-lymphocytes including OKT_4 -Leu3a $^+$ (helper/inducer) cells and OKT_8^+ (suppressor/cytotoxic) cells were also present. However, OKT_4 -Leu3a $^+$ cells were present in small numbers. Many OKT_6^+ cells were detected in the lesion area, indicating the presence of Langerhans cells. Langerhans cells function as antigen presenting and activating cells for T-lymphocytes.²⁹

Our data indicate that B-lymphocytes, T-lymphocytes, and Langerhans cells are involved, suggesting that other immune mechanisms in addition to type I reaction are participating in the pathogenesis of the disease and points to a complex immunopathogenesis. From our work we can conclude that humoral immunity and cell mediated immunity are involved. Other authors¹¹ suggested that delayed-type hypersensitivity of the cutaneous basophil type may be involved owing to the presence of basophils in conjunction with other pathological changes. In addition a non-IgE-mediated immune

mechanism involvement in the pathogenesis of the disease is suggested by the good response of the disease to corticosteroid therapy, by the poor clinical response to topical antihistamines, and by its resistance to sodium cromoglycate in some patients. Sodium cromoglycate acts by inhibiting the release of histamine and other mediators of immediate (type I) hypersensitivity reaction in mast cells, possibly by stabilising the cell wall membrane to changes in Ca^{++} ion permeability.³⁰ This variable clinical response of the disease to these lines of treatment can be explained by the complex immunopathogenesis of the disease as shown by our data.

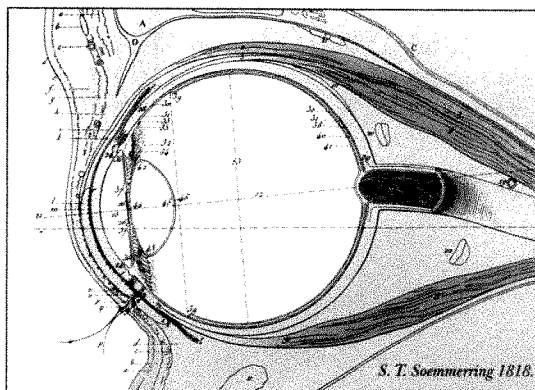
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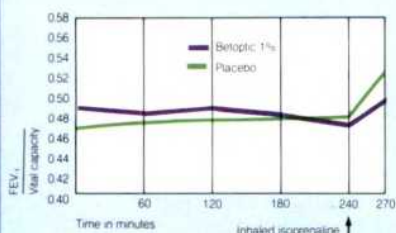
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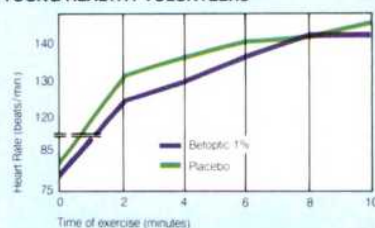
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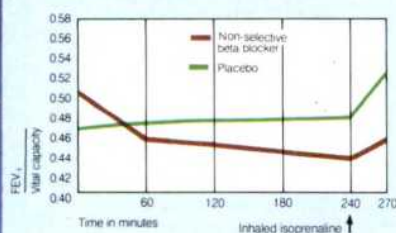


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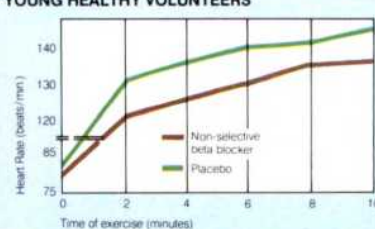
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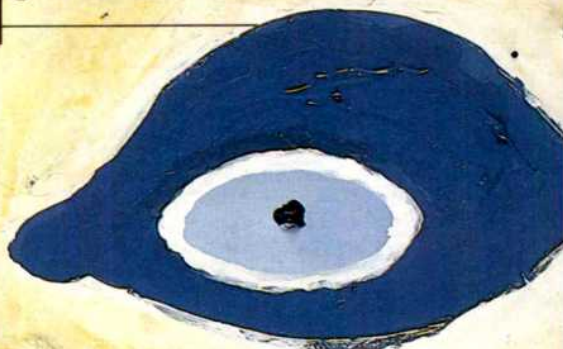
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IN HET OOG, UIT HET HART

Impact of cattle on the prevalence and severity of trachoma

G DE SOLE

National Programme for the Prevention of Blindness

SUMMARY Ethiopia is the African country with the largest number of cattle (26 million). Because of the potential impact of cattle on the transmission and severity of trachoma, the major cause of blindness in the country, an attempt is made to document this association to justify the inclusion of the control of cattle pollution in the prevention of blindness. The prevalence of trachoma is lower in pastoralists who herd mainly camels than in pastoralists who herd mainly cattle. In the first group the prevalences of moderate and severe trachoma in children under 10 are 0.9% and trichiasis/entropion in the total population 0.2%, whereas in the second group the prevalences are 45.1% and 4.0% respectively. In Borana pastoralists with and without cattle the prevalence ratio for moderate and severe trachoma is 1.0, whereas the prevalence ratios for severe trachoma and conjunctivitis were higher in the group with cattle, 2.5 and 3.0 ($p < 0.001$ for both). The elimination of cattle pollution should reduce the prevalence of severe trachoma by 45.4%. This is the first study presenting evidence of an association between cattle and trachoma. On the basis of this study a strong recommendation is made to the Ministry of Health to control cattle pollution in rural areas as a major strategy to prevent blindness in Ethiopia.

With an estimated prevalence of 0.7% blind in the total population, trachoma is the major cause of blindness in Ethiopia.¹ Cattle droppings, by exacerbating this problem, are believed to be associated with blinding trachoma. However, hard evidence has been lacking. Other domestic animals do not seem to play an appreciable part in the transmission of the disease. Droppings from goats and sheep are too small and dry. Transport animals are too few. Camel herds roam far from villages under the care of a few adults.

The Ethiopian Ministry of Health is strongly committed to improving sanitation in rural areas. However, it concentrates on latrine building. It is the belief of the author that in rural areas of Ethiopia control of pollution created by 26 million cattle² would be more effective than constructing latrines for the prevention of blindness caused by trachoma.

The following two studies were conducted to collect data supporting this opinion: (1) a comparison

of the prevalence of trachoma in pastoralists who mainly herd cattle and pastoralists who mainly herd camels; (2) a comparison of the prevalence of trachoma and conjunctivitis in the same pastoralist group, selecting one village with cattle and one that had lost its cattle in the recent drought.

Materials and methods

The decision to study Cusitic pastoralist groups was based on the high degree of homogeneity of this population. The three groups surveyed live in similar dry environments where pastoralist life is the only answer to successful survival if outside intervention is excluded. Pastoralist life itself does not allow much variation because of the harshness of the environment. Mobility is controlled by rain. Yearly variation of the rainfall is more important than variation between places. The three groups were all Moslem and lived in areas with two rainy seasons per year, averaging an annual precipitation of 400 mm.

For the first study Somali people from the Hiran region of Somalia were chosen to represent camel

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herders. They also keep a few cattle, less than one per family. A total of nine villages were randomly selected from the list prepared by the smallpox eradication campaign. Kereyu and Borana from Shewa and Sidamo regions of Ethiopia were chosen as cattle herders. Both groups also have small camel herds. A total of 19 Kereyu villages located in a 20 km radius from the town of Metahara were selected. Only four Borana villages were selected, two in the east and two in the centre of their territory. The only other Cusitic pastoralist group in Ethiopia, the Afar, was excluded because the Afars live in an ecologically different environment. The average size of the Somali villages was 24 children under the age of 10 per village. The average size of the Kereyu villages was 48 children under the age of 10 per village. The average size of the Borana villages was 206 children under the age of 10 per village.

To decrease the possible influence of factors not accounted for it was considered important to compare prevalences in the same ethnic group between villages with and without cattle. The present drought made this study possible. Two Borana villages of approximately the same size, 210 and 197 children under the age of 10, were selected. They are located in the central area of the Borana territory, the first with cattle near the town of Yabello, and the second without cattle near the town of Mega. The latter village was formed two years ago by families who had lost their herds. All families present had been living in the village for at least seven months. Both villages were surveyed, two days apart, at the beginning of the small rainy season. Characteristics of the two villages are given in Table 2. In all villages of the two studies the entire population under the age of 10 was examined. For the diagnosis of trachoma and conjunctivitis the 1981 WHO criteria were followed.³ These are:

Moderate trachoma: more than 5 follicles in the central tarsal plate (equivalent to WHO follicles grade F3).

Severe trachoma: papillae obscuring more than half the tarsal vessels plus follicles (equivalent to WHO papillae grade P3 and follicles grade F1 to F3).

Conjunctivitis: hyperaemia, purulent or mucoid discharge, frequent swelling of the lids and peri-orbital area.

Results

In Somali camel herders the prevalence of moderate and severe trachoma in children under 10 was 0.9%, and the prevalence of trichiasis/entropion in the total population 0.2%. These figures are below the cut-off points for hyperendemicity of 5% and 1% estab-

Table 1 *Prevalence of trachoma in three pastoralist groups: mainly Somali camel herders and mainly Kereyu and Borana cattle herders*

	Moderate+severe trachoma in children under 10	Trichiasis/entropion in total population
Somali	2/216 (0.9%)	1/ 499 (0.2%)
Kereyu	349/907 (38.5%)	82/2056 (4.0%)
Borana	427/825 (51.8%)	—

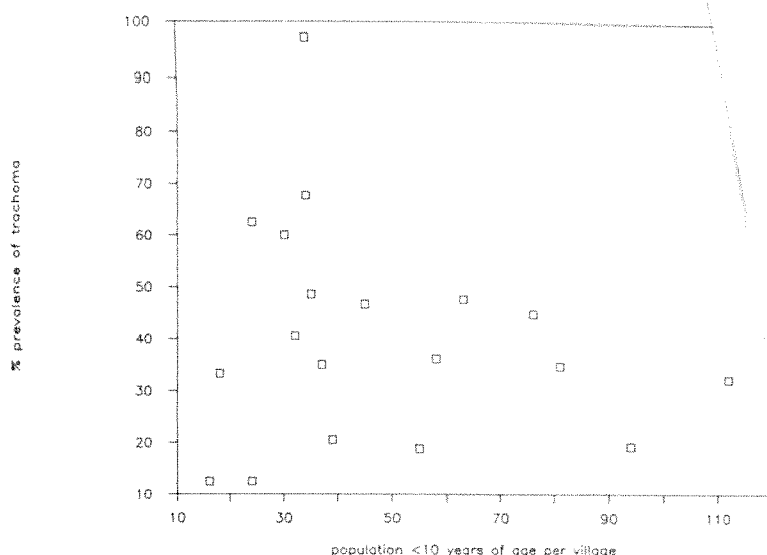
lished by the WHO.³ The prevalence of moderate and severe trachoma was 38.5% in Kereyu and 51.8% in Borana cattle herders. The prevalence of trichiasis/entropion in the total population was 4.0% in Kereyu people. No trichiasis/entropion data were collected for Borana people (Table 1). The difference between prevalences in camel and cattle herders was statistically significant ($p < 0.001$). In the 19 Kereyu villages surveyed, village size presented a statistically insignificant negative correlation of -0.0168 with prevalence of moderate and severe trachoma (Figure 1).

Table 2 depicts the prevalence of eye infections in Borana pastoralists with and without cattle. The prevalence of moderate and severe trachoma in children under 10 was 52.3% in the village with cattle and 53.3% in the village without cattle. The ratio of trachoma prevalences was 1.0. However the prevalences of severe trachoma and conjunctivitis were higher in the village with cattle, 29.9% and 15.2% respectively, than in the village without cattle, 15.2% and 5.0%. The prevalence ratio for severe trachoma

Table 2 *Characteristics of the Borana villages*

	Village with cattle	Village without cattle	Prevalence ratio
Size (no. of children under 10)	197	210	
Source of water	well	well	
Distance to water	<1 km	<1 km	
Housing	Round huts, no windows	Round huts, no windows	
Average shortest distance between houses	3 m	3 m	
Ethnic groups	Borano	Borano	
Nearest health centre	13 kms	15 kms	
Proportion of children examined with flies in eyes out of total examined	3/4 (75%)	1/5 (20%)	
No. of children under 10 examined	197	210	
Moderate+severe trachoma	103 (52.3%)	112 (53.3%)	1.0
Severe trachoma	59 (29.9%)	25 (11.9%)	2.5 ($p < 0.001$)
Conjunctivitis	30 (15.2%)	10 (5.0%)	3.0 ($p < 0.001$)

Impact of cattle on the prevalence and severity of trachoma



was 2.5 ($p < 0.001$). The prevalence ratio for conjunctivitis was 3.0 ($p < 0.001$).

Discussion

The three Cusitic pastoralist groups were chosen because of the homogeneity of their ecological environment and ways of life. The prevalence of trachoma is several times higher in cattle herder pastoralists than in camel herders. The disease is the major cause of blindness in the former group whereas it does not constitute a public health problem in the latter. Seasonality may account for part of the observed difference of active trachoma but does not influence the higher prevalence of trichiasis/entropion. In addition, on the assumption that the data on Somali people were collected during the month of lowest incidence, the 0.9% moderate and severe trachoma prevalence recorded can be compared with the lowest prevalence recorded in the survey of Kereyu people. The survey was conducted during three distinct periods before, during, and after the main rainy season. The lowest prevalence of 23.9% was recorded before the rains. It is 26 times greater than that of the Somali sample. Village size does not appear to influence the observed difference in prevalence. A statistically insignificant negative correlation was found in the Kereyu villages between prevalence and village size. The correlation coefficient was not calculated in the other two ethnic groups because of the small number of villages or low prevalence.

The second study indicates that there is an increased risk of severe trachoma (prevalence ratio

2.5) and conjunctivitis (prevalence ratio 3.0) when cattle are present. However, the presence of moderate and severe trachoma (prevalence ratio 1.0) remains uninfluenced. The high prevalence of active trachoma in the group without cattle is explained by the fact that they lost their herds only recently. For the same reason the difference in prevalence of severe trachoma and conjunctivitis reported may be considered an underestimate if their prevalence is expected to decrease in the group without cattle with prolonged lack of exposure to this risk factor.

However, it should be emphasised that the association described in this paper may not be entirely causal, but at least in part due to a confounding phenomenon.

These studies demonstrate the importance of cattle in the transmission and severity of eye infections. Even though the Tric agent infection alone can cause hyperendemic trachoma, it seems that bacterial infection is required in addition to give rise to blinding hyperendemic trachoma.⁴ This condition arises when eye-to-eye transmission is frequent in a situation of extreme ocular promiscuity, with flies adding to the spread of the disease.⁴ Cattle droppings, by increasing the number of flies, contribute to the transmission of blinding trachoma, as the increased risk of severe trachoma and conjunctivitis in this study indicates. Flies were seen on children's faces during the examinations far more often in the villages with cattle (3 out of four) than in the villages without (one out of five).

It appears, however, that neither cattle ownership nor the presence of cattle in the village has a major role in the size of the fly population. Instead, the

... seems to be the way in which the ... the Borana village with cattle each ... herd in a corral about 7 m in diameter ... the living quarters, from sunset to sun- ... corrals were filled with droppings and flies ... warming. The low level of personal hygiene of ... children worsened the situation. Flies were ... attracted by eye discharge and were allowed on the ... children's faces for several seconds, increasing the ... probability of carrying the infection to susceptible ... individuals.

This vicious cycle appears to be characteristic of children up to the age of 12 years. Persons over this age clean their faces regularly and wave flies away from their eyes. Cattle pollution and this vicious circle are not restricted to pastoralists, who constitute only a small percentage of the Ethiopian population, but are common for the majority of the mainly farming rural population of the country. On an estimate that 55% of the Ethiopian population is exposed to cattle pollution, the elimination of this factor would reduce the prevalence of severe trachoma lesions by 45.4%.

On the basis of these findings a strong recommendation is made to the Ministry of Health to include control of cattle pollution, in addition to

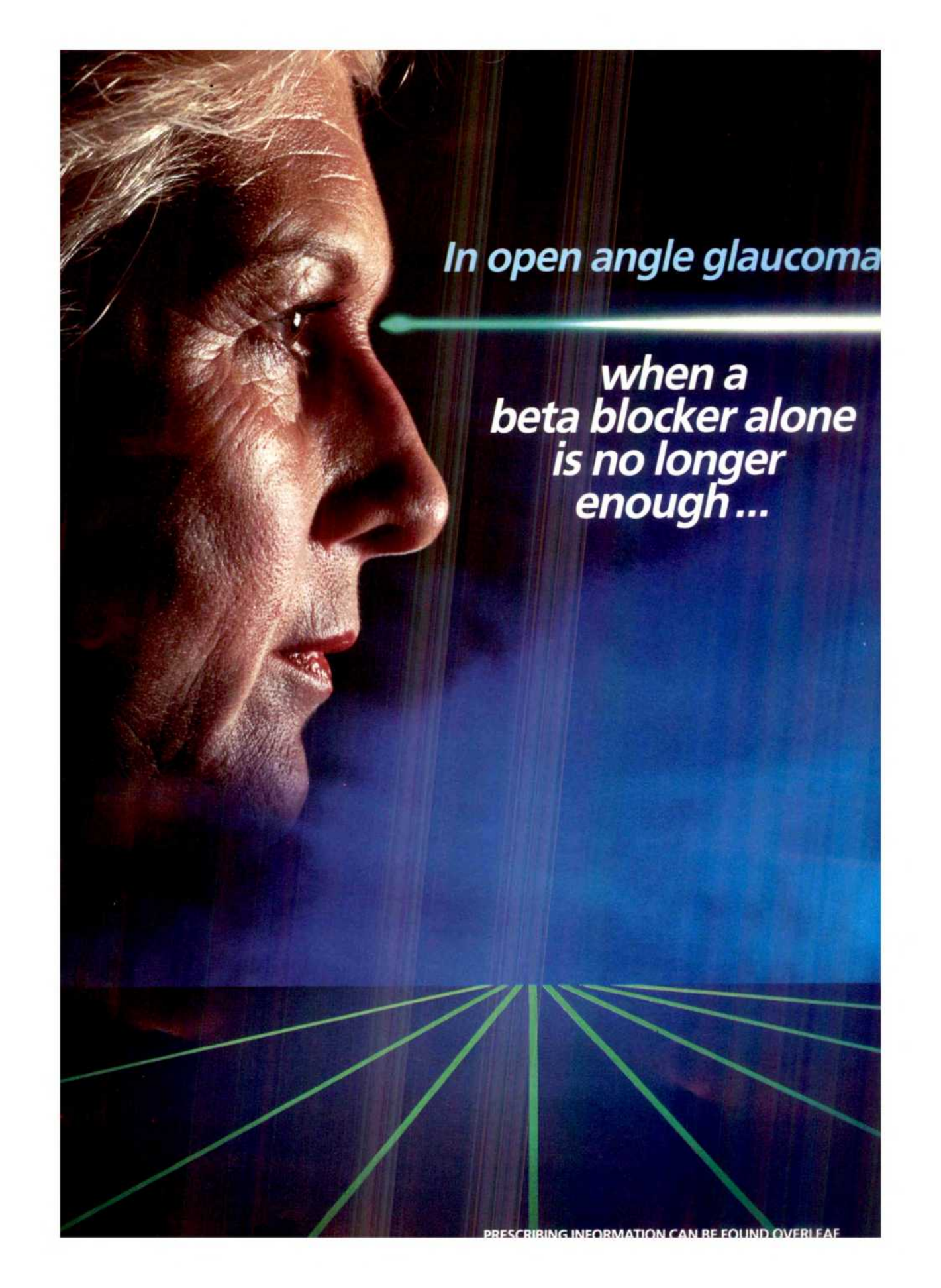
promoting improved personal hygiene⁵ especially of children under 12, to prevent blindness in rural areas. The construction of corrals distant from living quarters is suggested. Because of the programme of village construction in the country, it would be preferable to start implementing this strategy in the new settlements and attempt to modify old villages at a later date. Its implementation will also create conditions for prospective studies on the subject.

We are grateful to the Yaebello, Mega, and Metahara health centres for their kind collaboration.

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Postoperative grey-white lines of the posterior cornea and endothelial cell damage

HANIA C LAGANOWSKI, MALCOLM G KERR MUIR,
AND EMIL S SHERRARD

From the Department of Clinical Ophthalmology, Institute of Ophthalmology, and Moorfields Eye Hospital, City Road, London EC

SUMMARY 'Snailtracks' (grey-white streaks and patches on the posterior corneal surface which occur postoperatively) have recently been implicated as possible markers of corneal endothelial cell damage. We have examined this phenomenon in vivo with the slit-lamp and specular microscope. We recognised three types of linear form and, in contradiction of other observers, found that each was always coincident with a wrinkle in Descemet's membrane. Moreover, we were able to demonstrate only minimal endothelial cell damage in only a few of the tracks.

It seems probable that grey-white lines at the level of the corneal endothelium are a frequent phenomenon following extracapsular cataract extraction (ECCE) with or without intraocular lens (IOL) implantation, and perhaps other intraocular procedures. However, it appears that little regard has been paid to them, if and when noted, probably because of their transience and apparent lack of long-term significance.

Alfonso *et al.*¹ have recently drawn attention to these changes, calling them 'snailtracks' because of their slit-lamp appearance—that is 'irregular, discontinuous, greyish-white streaks or patches, usually oriented horizontally and obliquely, but also seen oriented vertically'.

On specifically seeking snailtracks with the slit-lamp these authors noted them on the first postoperative day in 42 out of 46 (91%) consecutive patients undergoing ECCEs. In order to determine the precise nature of the snailtracks they examined by scanning electron microscopy similar 'lesions' noted in a corneal button stored in McCarey-Kaufman medium and those induced in a human cadaver eye by ECCE. They found a gradation of endothelial cell changes culminating in irreversible cell damage and sloughing from Descemet's membrane. On this evidence they suggested that the presence of snailtracks in in-vivo eyes may 'have clinical relevance as a marker for corneal endothelial cell damage'.

The purpose of this study was to investigate further

the precise nature and significance of snailtracks and to support or otherwise the above contention of Alfonso *et al.* If snailtracks are markers of endothelial loss, they become of increasing concern as more ECCEs with or without IOL implantation are performed in young people, since early, acute loss of endothelial cells with consequent, subsequent accelerated age-related loss² may result in corneal decompensation later in life.

To eliminate the uncertainties of extrapolation from the in-vitro to the in-vivo state snailtracks of the corneal endothelium were studied with the slit-lamp and high magnification specular microscope in the living human eye. No attempt was made to determine their aetiology.

Material and methods

SLIT LAMP EXAMINATION

Snailtracks as defined by Alfonso *et al.*¹ were observed by careful slit-lamp examination in 20 patients after ECCE with IOL implantation. To determine their general characteristics various methods of illumination were used—for example, direct, retro-, and specular. In order to seek and examine vertically orientated snailtracks with the horizontal axis of the cornea parallel with the vertical slit-beam one patient was examined with her head sideways so that the vertical axis of the eye was horizontal.

The examinations were performed on the first and

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second postoperative days in all cases, and additionally on the fourteenth day in 10 cases.

SPECULAR MICROSCOPY

Following slit-lamp examination on the first postoperative day the endothelia of six of the cases were examined and photographed with the large-field specular microscope (Pocklington, Keeler/Konan). These same areas of endothelia were relocated, by reference to the posterior corneal rings,³ and examined on various subsequent postoperative days as indicated by the slit-lamp appearances.

MODEL

To aid the interpretation of the nature of snailtracks a simple model was constructed to mimic the posterior surface of the cornea.

A single layer of transparent polyethylene Cling-film was mounted over the mouth of a 20 mm diameter hollow cylinder such that it could be blown into a convex shape by air pressure from behind. Wrinkles were then induced in it by withdrawing a small volume of air. The wrinkled polyethylene was carefully examined with the slit-lamp.

Results

SLIT-LAMP APPEARANCE

Streak-like or linear tracks (Fig. 1) were found in all corneas examined with the slit-lamp on the first postoperative day. Their numbers varied from eye to eye and in general they were concentrated in the upper one-third to one-half of the cornea.

The intensity of horizontally and obliquely orientated linear tracks was variable. In some eyes some or all of them were extremely obvious and clearly visible with almost any setting of the slit-lamp, while in others they were very faint and could easily have been overlooked by the casual observer.

In some cases vertical tracks, although often vague, were also seen, and the result was an overall criss-cross pattern. When the cornea was examined with the horizontal axis of the eye parallel to the vertical slit beam, tracks with vertical orientation relative to the eye became more obvious than those with other orientations. This suggested that the apparent infrequency and indistinctness of vertical tracks is a function of illumination.

The linear tracks showed straight, curved, and even hooked forms and were either continuous or segmented (Fig. 1).

They measured from approximately 0.1 mm to 8 mm in length and 0.1 mm to 0.5 mm in width, as determined from slit-lamp photographs.

Many of the tracks had a distinctly granular appearance and irregular edges (Fig. 1). They either

appeared white and suggested endothelial changes, or had a yellowish tinge with scattered pigment suggesting the deposition of fine particulate matter (which was observed circulating in the aqueous humour in all eyes). Other tracks were grey and agranular with straight margins. In many cases the appearance of a single track varied along its length with white-granular and agranular segments.

It was found that the use of a broad slit beam at right angles to the axes of the viewing system and of the forward gazing eye revealed the linear tracks of all types to the best effect (Fig. 1). When the area of the cornea in view was illuminated by a beam directed more or less parallel to its surfaces, these tracks appeared as described. However, when the same area was illuminated at right angles to its surfaces, the tracks appeared as wrinkles in the posterior cornea, and small patches of specular reflection from their edges were evident—usually where two tracks at different orientations crossed. By changing from one direction of illumination to another it could always be shown that linear tracks of all orientations were wrinkles and vice versa (Fig. 2a, b).



Fig. 1 Slit-lamp photograph, with broad beam illumination at 90°, of cornea showing granular, linear tracks one day after ECCE/IOL.

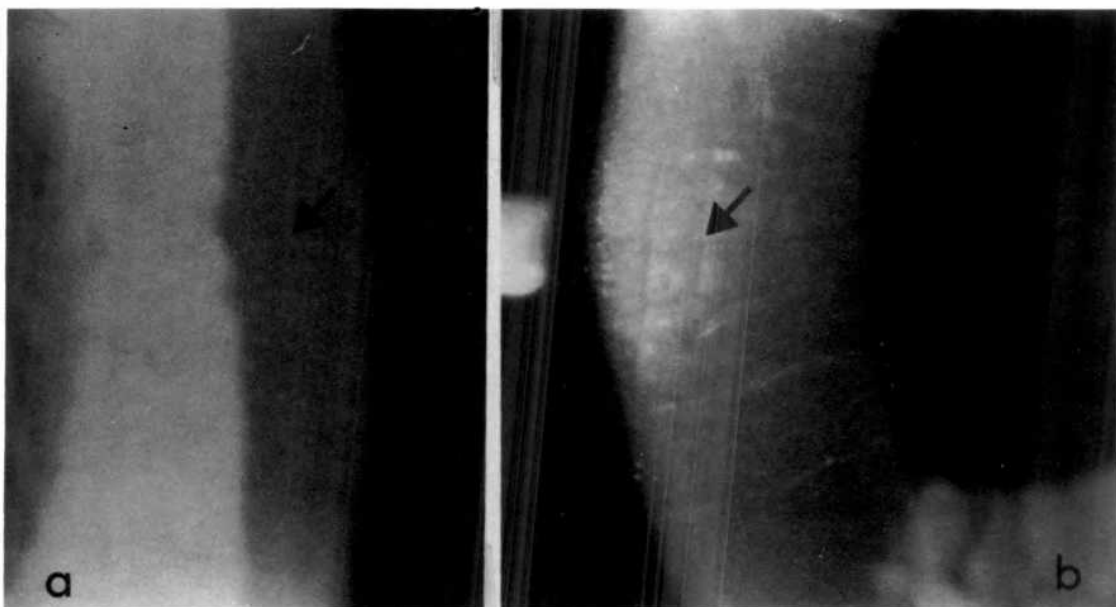


Fig. 2 Slit-lamp photographs of cornea with linear tracks. (a) With illumination parallel to corneal surfaces the tracks appear as greyish-white lines. (b) Same area as (a) with illumination at right angles to corneal surfaces the tracks appear as wrinkles in the posterior cornea. (Arrows indicate same point in (a) and (b)).

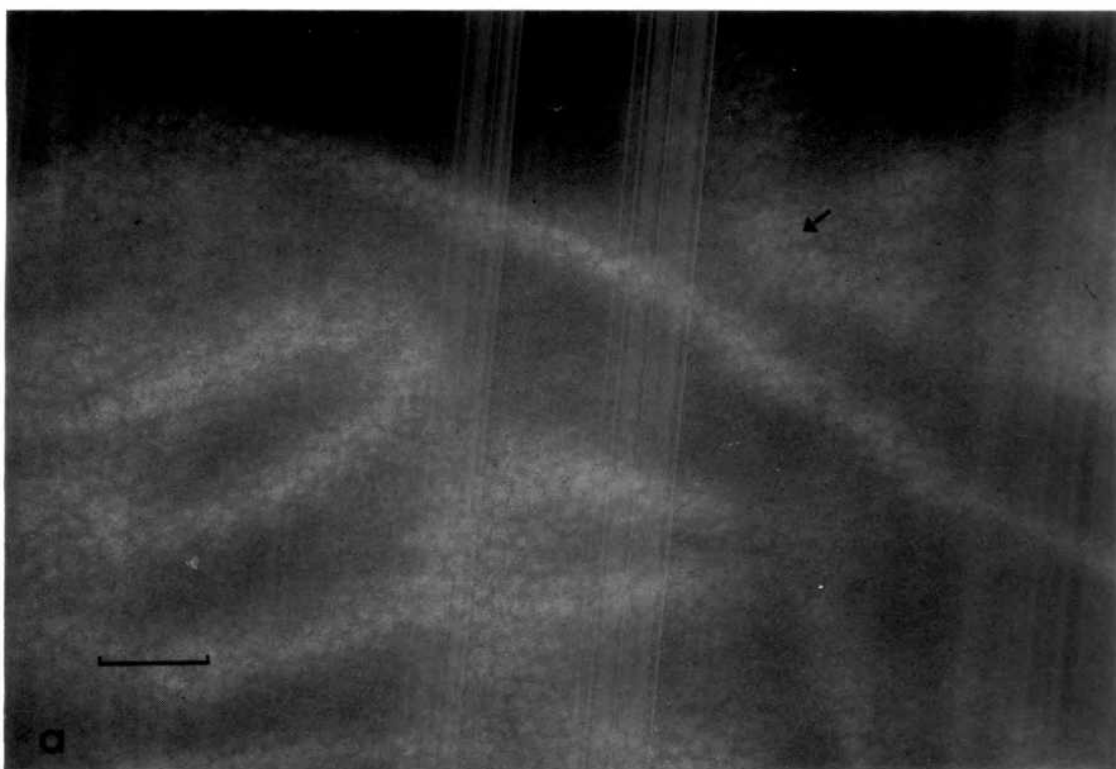


Fig. 3 a

Fig. 3 Specular photomicrograph of endothelium one day after ECCE/IOL. Bar=0.1 mm. (a) With normal pressure of applanation—excessive wrinkles are present. (b) Same area as (a) with greater pressure of applanation—most of the wrinkles are no longer apparent. (Arrows indicate same cell in (a) and (b)).

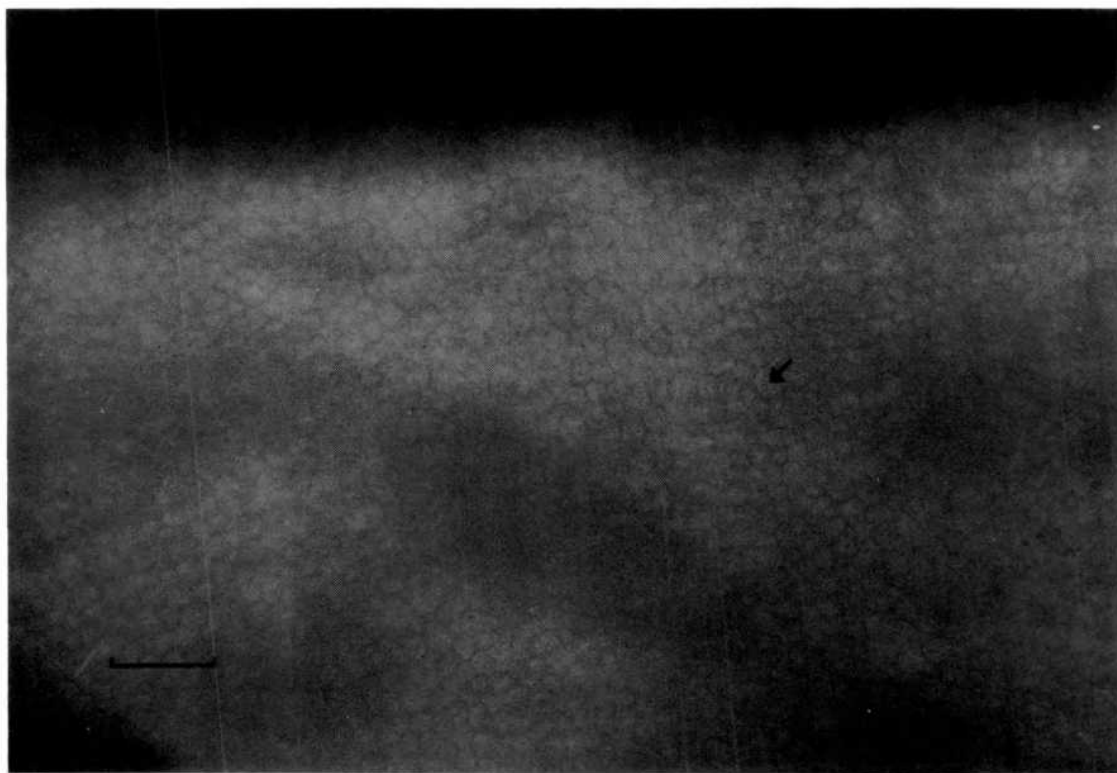


Fig. 3b

In many instances there were a few blotch-like patches, distinct from the linear tracks, on the posterior corneal surface. These had a similar 'texture' to the yellow-tinted, linear tracks and an appearance suggesting deposition of particulate matter. They were not coincident with detectable distortions of Descemet's membrane.

On the second postoperative day there was little change in the tracks in many cases. However, some of the previously elongated granular forms had broken up into irregular segments separated by agranular sections, and in a few cases only small, scattered, opaque segments remained. Many of the blotch-like patches had disappeared.

Tracks were still present in three of the 10 eyes two weeks postoperatively.

MODEL

On examining the polyethylene model with direct illumination and viewing, grey-white lines similar to agranular linear tracks were visible in the otherwise transparent membrane. However, on moving the model relative to the slit-lamp the true nature of these lines—that is, the sloping sides of wrinkles—was easily demonstrated by achieving specular reflection from their edges and troughs or crests.

SPECULAR MICROSCOPY

In all six eyes examined with the specular microscope on the first postoperative day excessive numbers of shallow wrinkles of the posterior corneal surface were seen (Fig. 3a). These were consistent in both number and orientation with the linear tracks seen with the slit-lamp on the same occasion. There were, however, surprisingly few instances of endothelial change or particulate deposits associated with them. This might have been because any changes were hidden in the dark area of the wrinkles (Fig. 3a). However, it was possible in most cases to flatten some of the wrinkles by applying more pressure with the applanating objective, and render visible the endothelium previously incorporated in them; this revealed normal endothelium in most instances (Fig. 3b).

Where changes were observed, the endothelial mosaic was greatly distorted along much of the length of the wrinkle. This was mainly due to elongation of the cells in two or three rows, with the long axes of the cells orientated obliquely towards the long axis of the wrinkle, giving a pinnate arrangement (Fig. 4). Along some wrinkles there were groups of elongated cells radiating from a point which were separated by normal cells.

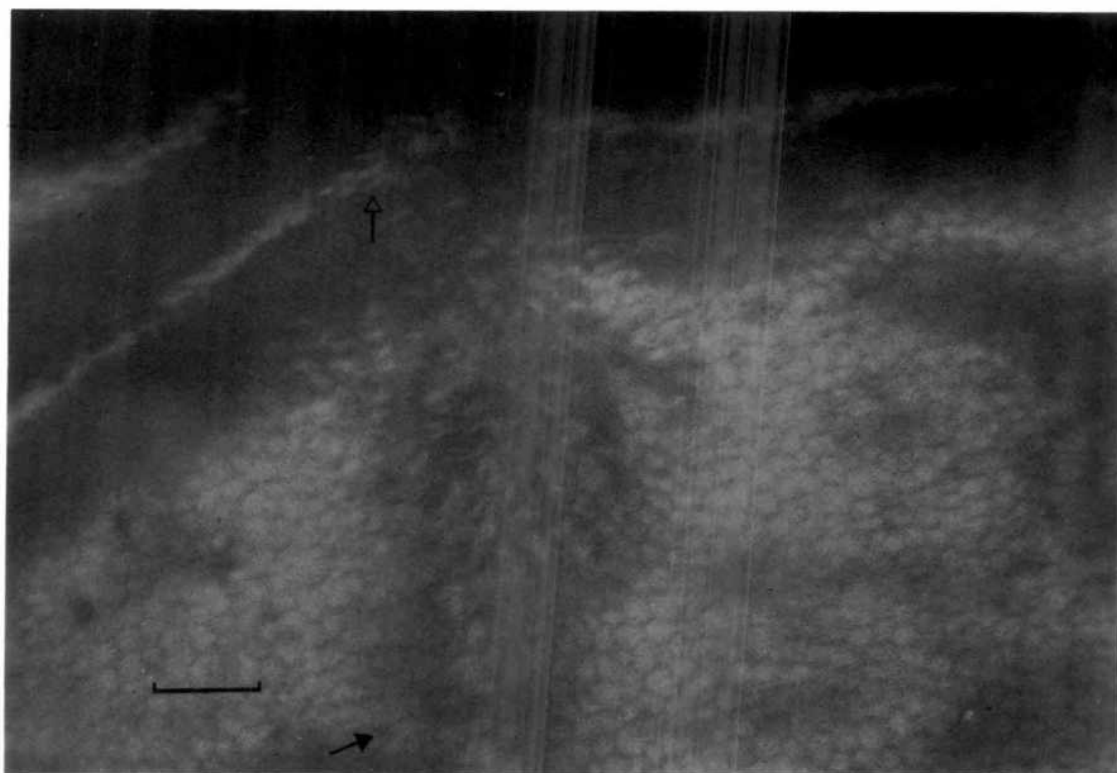


Fig. 4 Specular photomicrograph of endothelium one day after ECCE/IOL showing pinnate arrangement of elongated cells along a vertical wrinkle. A rosette (solid arrow) and a group of spindle-shaped cells (open arrow) are present. Bar=0.1 mm.

In two eyes similar but non-linearly distributed changes were seen which were not associated with wrinkles (Fig. 5).

On a smaller scale rosettes (a group of neighbouring cells elongated to a common point) were numerous within the altered areas (Figs. 4, 5). There were occasional groups of thin spindle-like cells (Fig. 4) and many cells possessed inclusions—probably vacuoles (Fig. 5).

Away from the altered areas, even within the wrinkles, the endothelium showed normal polymegethism in four of the eyes, and was composed of slightly enlarged regular cells in the other two.

The specular microscope, in either the specular or the relief mode,⁴ failed to demonstrate the presence of fine granular deposits in linear form, but in some cases generalised deposition of fine material in the entire lower half of the cornea was noted in the relief mode.

On the second postoperative day wrinkles were observed as before but were more easily flattened. Along the course of those wrinkles which had previously shown distortion of the endothelial mosaic there were discontinuous areas containing endo-

thelial cells of bizarre shapes and sizes, many being larger than those found elsewhere. Rosettes were more common than on the previous day, but only a few cells now possessed inclusions. Between the patches of deformed cells, but still along the course of the wrinkle, the endothelium appeared normal.

In the one case examined with the specular microscope 14 days postoperatively no endothelial abnormality was detected on any of the flattened wrinkles or elsewhere, even though limited cell damage had been seen on the first postoperative day.

Discussion

Greyish white streaks and patches at the level of the endothelium, which by definition are 'snailtracks', were seen in all the corneas after ECCE with IOL implantation, although their number, pattern, and character varied.

Alfonso *et al.*¹ made the unsupported statement that 'snailtracks can be easily differentiated from Descemet's folds'. Our slit-lamp examinations showed that linear tracks were always coincident with wrinkles (small folds) and only the blotch-like

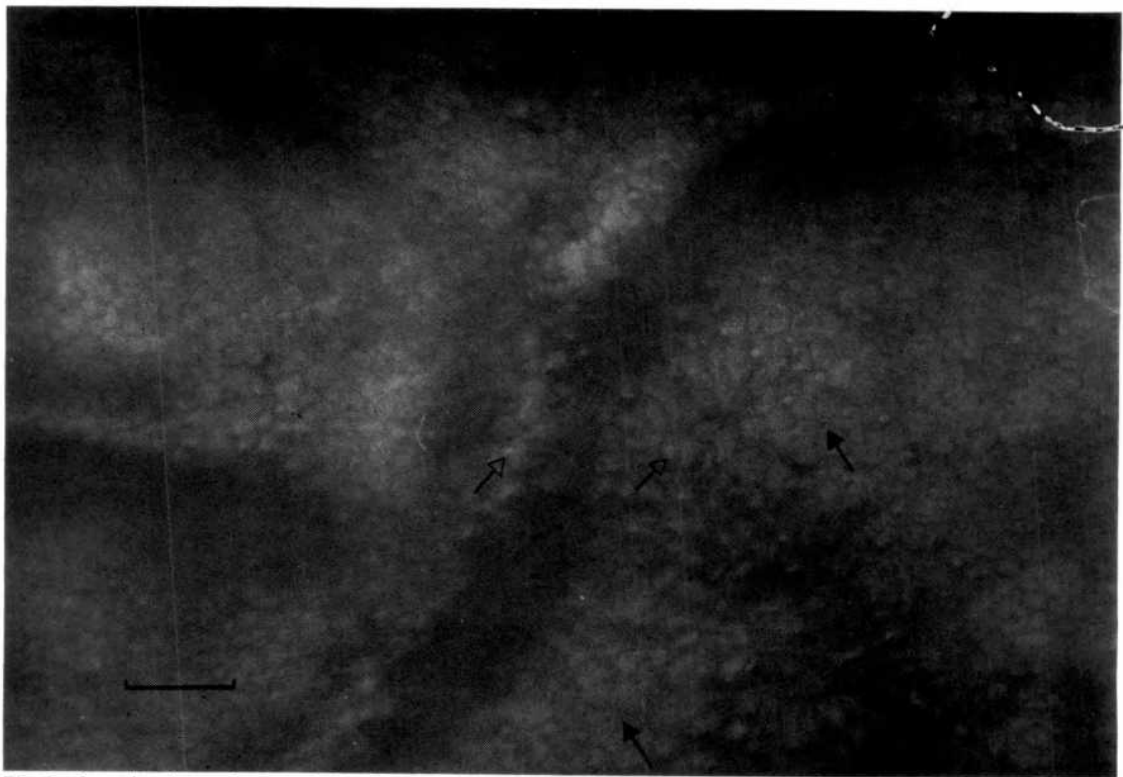


Fig. 5 Specular photomicrograph of endothelium one day after ECCE/IOL showing non-linear area of altered cells, rosettes (solid arrows), and cells with inclusions (open arrows). Bar=0.1 mm.

patches (which we note are included in the original description of 'snailtracks') were not. Whereas in some cases it was obvious that the tracks were wrinkles, in others this was difficult to demonstrate, but was consistently confirmed by achieving specular reflection from the edges of the wrinkles. Specular microscopy confirmed that the linear tracks were wrinkles.

It is our contention that all linear tracks are small wrinkles of Descemet's membrane. Because of their extreme shallowness the slit-lamp appearance of greyish white lines dominates, and the presence of a wrinkle often becomes apparent only on achieving specular reflection from its edges and trough or crest. In the case of large wrinkles the reverse is true; the wrinkles are obviously wrinkles and it is necessary to 'become aware' that their sloping sides actually appear as greyish white bands.

As in the polyethylene model, some of the wrinkles appeared with direct illumination as greyish white, otherwise featureless streaks. Others had a definite granular appearance, and two types were recognisable—white, which suggested damaged endothelial cells, and yellow tinted, which looked like adherent debris.

On rare occasions specular microscopy revealed endothelial changes which in some cases were consistent with irreversible cell damage. It has been shown experimentally that a rosette results from the loss of a single cell and that cells around the void extend processes into it to re-establish continuity of the endothelium within a matter of hours.⁵ Spindle-like rosettes have been seen within hours of known cell loss resulting from Nd/YAG laser procedures.⁶ Intracellular vacuoles are a sign of current disturbance of affected cells.⁷ Enlargement and distortion of cells is considered a late sign of cell loss.⁸

Specular microscopy did not confirm the slit-lamp impression of localised deposition of fine debris, either in linear or in patch form.

While it is tempting to conclude that (1) the simple wrinkles without associated endothelial change, as seen with the specular microscope, are those tracks that appear agranular with the slit-lamp, (2) those with endothelial damage are granular tracks, (3) those with discontinuous areas of endothelial damage are segmented tracks, and (4) the areas of endothelial change not associated with a wrinkle are the blotch-like patches, these relationships could not be con-

firmed, because no track of any particular slit-lamp appearance was knowingly examined by specular microscopy. Nevertheless, some of the corneas examined with the specular microscope were known to have a predominance of granular tracks, and there was therefore a strong probability that many of the wrinkles seen by specular microscopy were granular tracks, and yet only occasionally was endothelial damage found.

In general our slit-lamp impressions did not correlate with our specular microscopical findings, possibly because either our interpretations of the slit-lamp images were incorrect or the specular microscope failed to resolve the features they suggested.

Although our in-vivo observations have done little to elucidate the true nature of snailtracks, there is no doubt that endothelial damage is present in parts of some of them. However, because the majority of tracks show normal endothelium, they cannot be regarded as markers of endothelial cell damage.

While the linear tracks are basically wrinkles, the blotch-like forms are not associated with any detectable distortion of Descemet's membrane and they cannot therefore be regarded as the same entity. Moreover, in our experience snails are not prone to

creating random blotch-like tracks and we would therefore favour reserving the term 'snailtrack' as descriptive of the linear forms only.

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Book reviews

Basic and Advanced Vitreous Surgery. Eds. G BLANKENSHIP, S BINDER, M GONVERS, M STIRPE. Pp 419. DM 175. Springer-Verlag: Heidelberg. 1986.

The proceedings of a vitreous surgery course held in Rome in 1984 in memory of Dr G B Bietti have been published as the second volume in the Fidia research series which aims to promote 'rapid and worldwide dissemination of up-to-date interdisciplinary data'. Notwithstanding the failure of the book to meet these lofty aspirations, together with its somewhat pretentious title, there are nevertheless some rather readable reviews and vignettes from an international cast of participants which make this a very pleasant vitreoretinal tome in which to browse.

DAVID MCLEOD

Manual of Common Ophthalmic Surgical Procedures. Edited by CHARLES D PHELPS. Pp. 189. £33.00. Churchill Livingstone: Edinburgh. 1986.

This book, as the name suggests, is a compilation of basic surgical techniques, written by 16 ophthalmologists who have trained or at present work at the University of Iowa. Each surgical procedure is briefly introduced and an outline of its goals and principles, its preoperative management, and the preferred type of anaesthetic given. The reader is then guided through each operation in a detailed step-by-step fashion, and given the benefit of the authors' personal preferences and of practical 'pearls'. Most of the text is accompanied by excellent line drawings. These, however, vary in number from 22 in one chapter ('Penetrating keratoplasty'), to none at all in another ('Lens procedures').

My only criticism is that in most chapters, there is no mention of alternative surgical approaches or of the management of complications. All in all there is no doubt that this is a very useful book, and being reasonably priced it should be at hand for every ophthalmologist in training.

Z J GREGOR

Ophthalmic Microsurgery: Instrumentation, Microscopes, Technique. By J DRAEGER. Pp. 184. £67.50. Karger: Basel, Switzerland. 1987.

This book gives a comprehensive account of the development and use of equipment specifically designed for intraocular surgery. Technical aspects—for example, the solving of problems in introducing microsurgery and laser surgery to the posterior segment—are given added clarity by detailed illustrations and diagrams. The author himself has experience in the field of microsurgery stretching for more than 25 years. It is therefore an authoritative book and is written with the help of other specialists to cover such sections as the management of proliferative vitreoretinopathy.

It is not essential reading for the average ophthalmic surgeon, but for those with responsibility for setting up operating departments or for those with a special interest in some of the modern gadgetry that is now available the book will be found to be most rewarding.

S P B PERCTVAL

Note

What's new?

The New Orleans Academy of Ophthalmology will hold its 37th Annual Symposium on 'What's new in ophthalmology?' on 20–22 February 1988 at the Hyatt Regency, New Orleans, USA. Details from Emily Busby, Executive Secretary, New Orleans Academy of Ophthalmology, Eye, Ear, Nose and Throat Hospital, 145 Elk Place, Room 203, New Orleans, LA 70112, USA.

Correction

Associate Professor W S Hunter informs us that his initials should have been printed as shown here and not as in the title of the paper by R G Devenyi, G E Trope, and W H Hunter, *Br J Ophthalmol* 1987; 71: 441–4.

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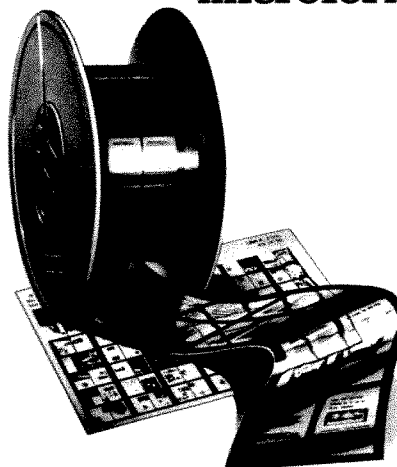
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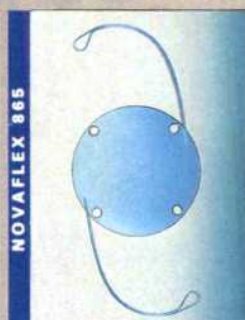
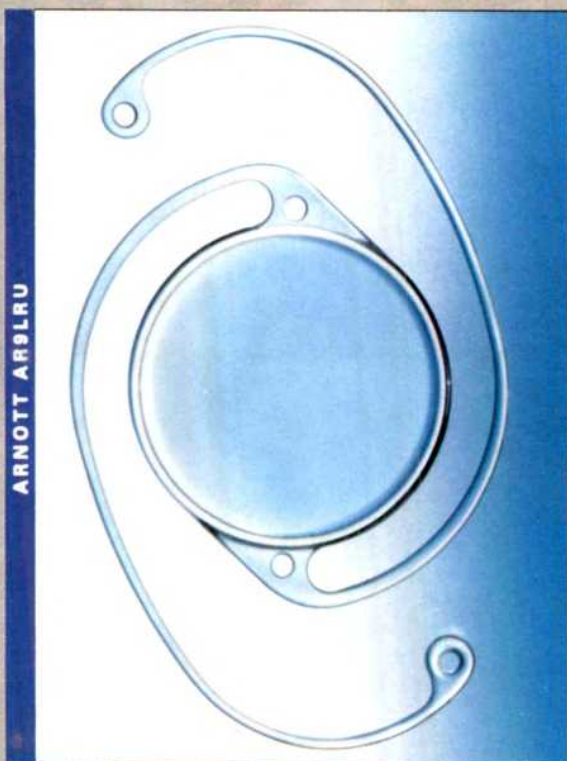
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E U R O P E S N E W N O 1

A photograph of an elderly woman with short, light-colored hair, wearing a white nightgown, sitting up in bed. She is holding a newspaper and looking towards the left. The room is dimly lit, with a bedside lamp and a clock visible on a table next to her. A window with curtains is on the left.

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Editorial: Disc damage and raised IOP

Although the relationship between raised intraocular pressure and optic disc damage in primary open-angle glaucoma remains enigmatic, we naturally suspect that some sort of relationship does exist. Most attempts to establish the relationship have involved studies of the pressure in its relation to visual field decay or to visible deterioration of the disc by photography, but there has not been much success so far in finding histopathological evidence to link pressure with disc change. Indeed Miller¹ even went so far as to suggest there was not necessarily a causal link but that disc damage and raised pressure might simply be associated symptoms caused by a third factor. Miller's suggestion was a vascular abnormality which by affecting the outflow system caused aberrations in pressure or by affecting the disc caused typical glaucomatous damage. It would not be surprising if such a (hypothetical) abnormality were to affect both anterior and posterior segments of the eye simultaneously, giving rise to the familiar combination of raised pressure and disc damage in ordinary primary open-angle glaucoma.

There are great difficulties in dismissing raised pressure as a cause of disc damage, since in many cases of secondary glaucoma and indeed in primary angle closure it obviously is the cause of the damage. Nevertheless the notion is attractive.

But does the common factor have to be a vascular anomaly? How would it be if an abnormality were to be present in the collagen both of the trabecular meshwork and of the lamina cribrosa? Might not this

give rise to weakness and consequent malfunction of the meshwork and at the same time weakness of the lamina cribrosa with obvious consequences.

The paper in this issue by Rehnberg, Ammitzböll, and Tengroth takes a small step forward in the process of establishing this possibility. In essence what the authors claim to have shown is that the characteristics of the collagen in the lamina cribrosa and trabecular meshwork are similar to one another but different from the sclera. Admittedly this study is on normal eyes only, but one awaits with great interest some evidence of possible variation from the normal in cases of glaucoma.

The search for a true step forward in chronic glaucoma has been a long and a weary one. The literature is full of painstaking efforts to relate the minutiae of visual field changes, whether computerised or not, to cleverly managed statistical manipulations of the intraocular pressure from the point of view of its mean, its peaks, its maximum, and its swings, not to mention a host of 'risk factors'—many of dubious relevance: but so far it has got us nowhere. It will certainly be a red letter day when someone can produce solid evidence to explain the peculiar discrepancies between pressure and field decay which we find so enigmatic at the moment.

REDMOND SMITH

Reference

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Collagen distribution in the lamina cribrosa and the trabecular meshwork of the human eye

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SUMMARY Tengroth and Ammitzböll found the collagen content of the optic disc in glaucoma to differ from that of normal eyes. A theory was advanced that a primary collagen disturbance might be involved in the pathogenesis of glaucoma. The connective tissue in the body has a supportive function in almost all the organs. The tensile strength and elasticity of connective tissue is mainly due to the presence of collagen fibres and elastic fibres, which also maintain the shape of the tissues. There are many different types of collagen, three of which are discussed in this paper. Type I collagen is found in tendons, skin, and numerous other organs, for example the eye. Type III is found mainly in the blood vessels but is also present in other tissues with a mesodermal origin, and type IV is found in the basement membranes. To elucidate the precise distribution of collagen types in the ocular structures an immunohistochemical study was undertaken in normal human eyes. The amino acids proline, hydroxyproline, and hydroxylysine, which are characteristic of collagen, were also analysed. Collagen types I, III, and IV were found in the lamina cribrosa, the trabecular meshwork, and the retrolaminar optic nerve. In contrast, only type I was found in the sclera.

Two structures which are of particular importance in connection with chronic open angle glaucoma are the trabecular meshwork and the lamina cribrosa. The hypothesis has been advanced that abnormalities in the composition of collagen, which provides the supportive framework, might cause decreased pressure resistance in these tissues. The result might be cupping of the optic disc and closure of the trabecular mesh, which in turn would cause strangulation of the nerve fibres and an increased outflow resistance.

In a previous study¹ the amounts of the collagen-specific amino acids proline (Pro), hydroxyproline (Hyp), and hydroxylysine (Hyl) in the trabecular meshwork, the lamina cribrosa, and the sclera of glaucomatous and normal human eyes were analysed. Significantly increased concentrations of Hyp, Hyl, and Pro were found in the optic disc of glaucomatous eyes, but the concentrations of the three amino acids in the trabecular meshwork and the sclera were found to be unaltered.

In the same study the collagen amino acid relationship, as reflected by the Hyp to Hyl ratio, was found

to be different in the trabecular meshwork, the optic disc, and the sclera. The lamina cribrosa, however, had not been separated from the retrolaminar tissue.

In the present study the lamina cribrosa has been isolated from the retrolaminar tissue, and the amino acid ratios of hydroxyproline (Hyp) and hydroxylysine (Hyl) have been determined for the trabecular meshwork, sclera, lamina cribrosa, and retrolaminar optic nerve. Differences between tissues in the ratios of these amino acids indicate that the tissues have different collagen compositions, although the amino acid ratios cannot be used to determine which types of collagen are present. Three types of collagen are of interest, namely, types I and III, which are interstitial collagens, and type IV, which is a basement collagen. We have therefore used antibodies to collagen types I, III, and IV with the peroxidase-antiperoxidase (PAP) technique to study the collagens immunohistochemically in the same four types of tissues that were used for the amino acid analysis.

The aim of this study was to characterise the collagen types in the lamina cribrosa and the trabecular meshwork and to determine whether

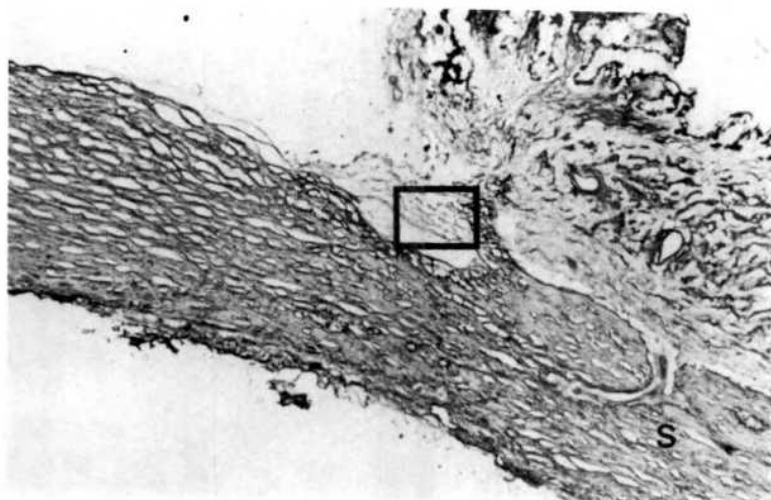


Fig. 1A

these structures have similar collagen compositions which differ from the collagen composition of the surrounding sclera in the normal human eye.

Material and methods

IMMUNOHISTOCHEMISTRY

Material. Ten normal eyes from persons aged 60 or more were obtained at necropsy, sectioned, and snapfrozen in liquid nitrogen (-80°C) and stored at -20°C . Affinity-purified rabbit antibodies to bovine type I (calf skin) collagen, type III (human amnion) collagen, and type IV (human placenta) collagen were used.*

*The antibodies were kindly made available by Professor Furthmayr, Yale University, USA.

Fig. 1A–F A: Region of the trabecular meshwork. B: Insert. The trabecular meshwork (TM) is weakly stained by antibodies to type I (Fig. 1A) but strongly stained with antibodies to type III (Figs. 1C, D) and type IV (Figs. 1E, F), both showing staining of the peripheral portion of the trabecular beams. The sclera (S) is stained with antibodies to type I collagen (Figs. 1A, B) but not type III (Figs. 1D, E) or type IV (Figs. 1E, F) with the exception of vessels.

Methods. Sections 6–8 μm thick of the tissue samples were cut with a cryostat and dried on to glass slides. The sections were pretreated with cold acetone for 5 min, incubated with phosphate buffered saline (PBS) for 5 min, and incubated with rabbit antibodies to type I collagen 1:4, type III collagen 1:200, and type IV collagen 1:200 in a moist chamber for 30 min at room temperature. The

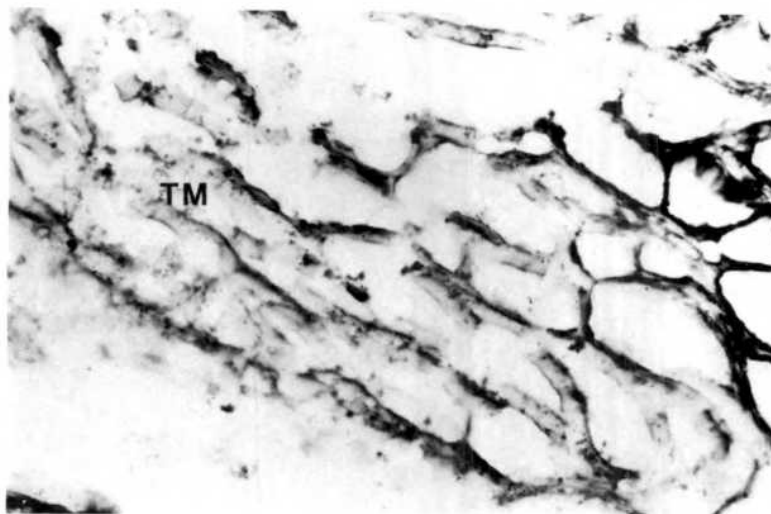


Fig. 1B Insert in Fig. 1A.

Fig. 1C

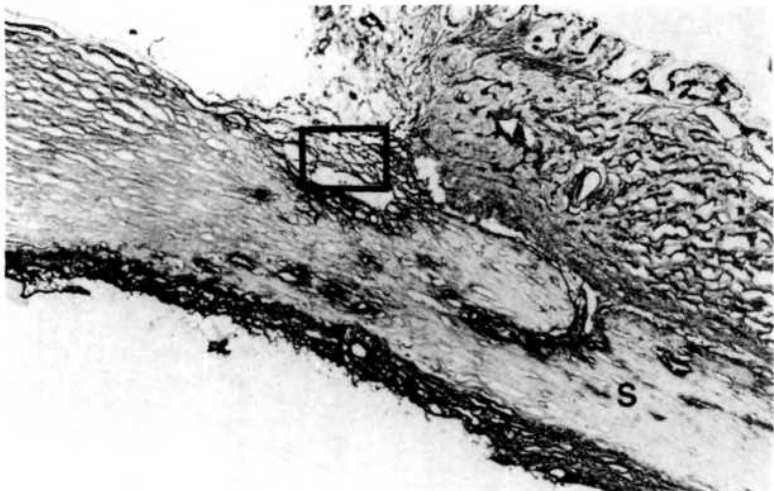


Fig. 1D *Insert in Fig. 1C.*

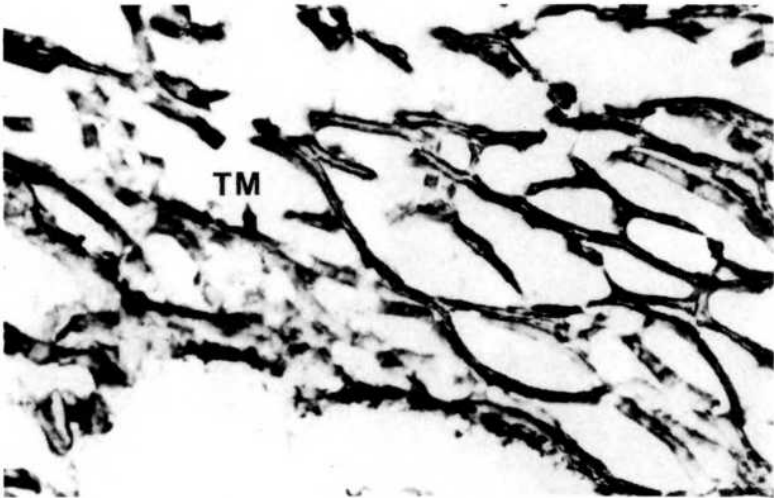
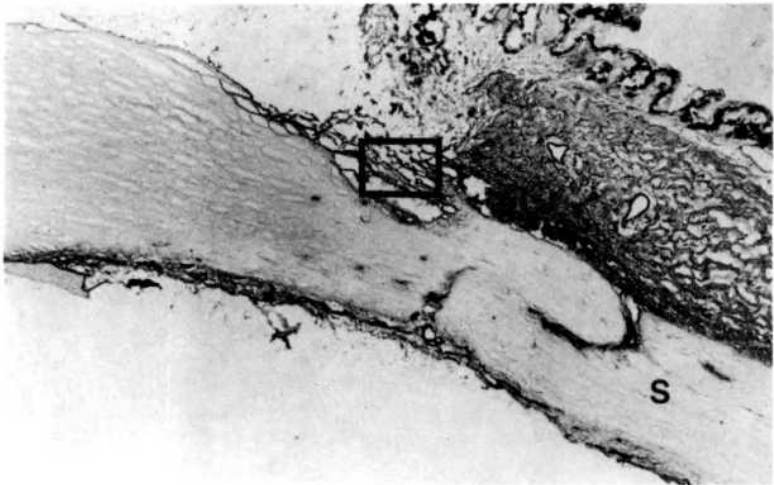


Fig. 1E



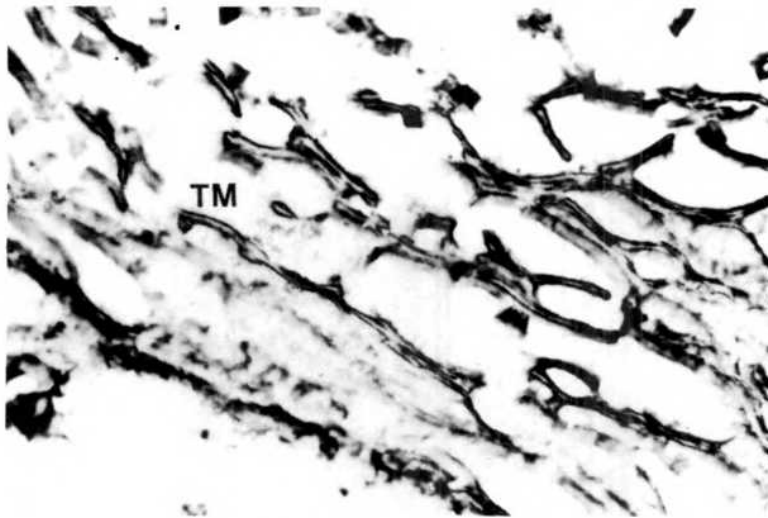


Fig. 1F Insert in Fig. 1E.

sections were then rinsed several times in PBS and subsequently stained with peroxidase-labelled anti-rabbit IgG and goat IgG for 30 min, rinsed again several times in PBS, stained with diaminobenzidine for 3–5 min, and mounted in glycerol. As a control PBS buffer was used instead of primary antisera.

AMINO ACID ANALYSIS

Material. Four normal eyes taken at necropsy from

two persons aged over 60 within 24 hours of death were used.

Methods. The eyes were dissected under a dissecting microscope and samples were taken from the trabecular meshwork, the sclera, and the lamina cribrosa as well as from the retrolaminar structures of the optic nerve.

The trabecular meshwork was excised with a fine pair of scissors in Schlemm's canal with extension along the Schwalbe line. The lamina cribrosa was dissected from the subarachnoid space to where it ends at the fusion of the pia and dura mater, the optic nerve being cut transversely with a razor blade and the lamina cribrosa excised from the sclera with a trephine.

The retrolaminar intrascleral part of the optic nerve was obtained, and a sample of scleral tissue

Fig. 2A–C Optic nerve head. The lamina cribrosa is strongly stained with antibodies to type I (Fig. 2A), III (Fig. 2B), and IV (Fig. 2C). Types I and III show similar stromal staining, whereas type IV stains the basal membrane. The optic nerve (ON) is strongly stained with antibodies to types I (Fig. 2A), III (Fig. 2B), and IV (Fig. 3C) in a similar fashion to the lamina cribrosa.

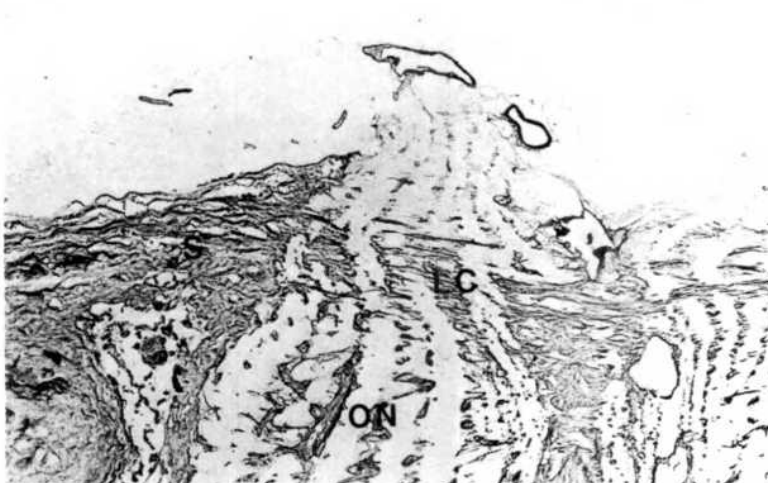
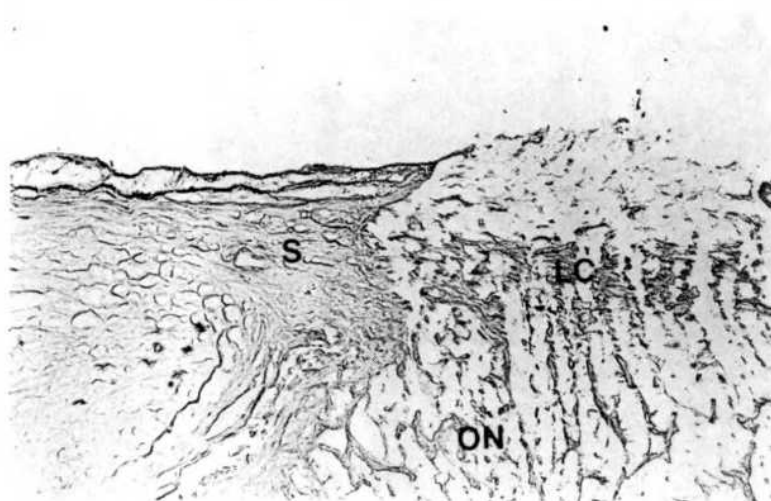


Fig. 2A

Fig. 2B



adjacent to the optic nerve was taken. The samples were stored in acetone. The collagen analysis was performed by measuring the concentrations (nmol/mg defatted dried tissue) of Hyp, Hyl, and Pro in samples of trabecular meshwork (T), lamina cribrosa (L), optic nerve (O), and sclera (S) as previously described.¹

Results

IMMUNOHISTOCHEMISTRY

In the adult eye the immunohistochemical findings indicated the presence of types I, III, and IV collagen in both the trabecular meshwork and the lamina cribrosa (Figs. 1A–F, 2A–C). Types III and IV showed strong, consistent staining in both these tissues, whereas type I showed strong staining in the

lamina cribrosa but somewhat weaker staining in the trabecular meshwork.

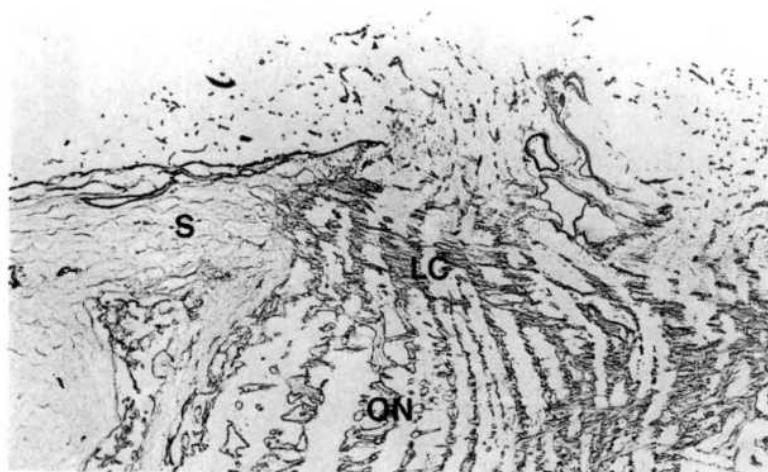
The sclera stained strongly for type I collagen but not for types III and IV. The optic nerve stained for types I, III, and IV collagen.

Fig. 3 shows the distribution of collagen types in a schematic eye.

AMINO ACID ANALYSIS

The mean range of the concentrations of Hyp, Hyl, and Pro (nmol/mg defatted dried tissue) were recorded (Table 1), and the molar ratio of Hyp to Hyl was calculated (Table 2 and Fig. 4). In all four eyes the highest concentration of Hyp, Hyl, and Pro was found in the sclera and the lowest concentration in the lamina cribrosa. The Hyl concentration was almost equal in the sclera and the trabecular mesh-

Fig. 2C



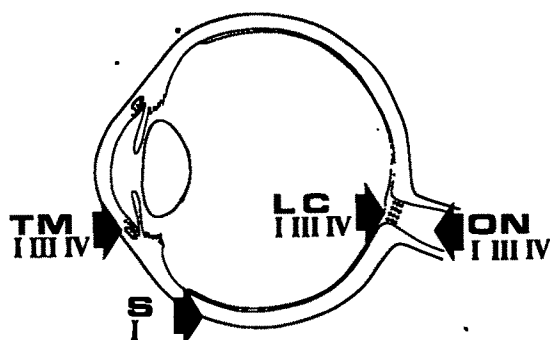


Fig. 3 The collagen types I, III, and IV were found in the trabecular meshwork (TM), lamina cribrosa (LC), and the optic nerve (ON). Only type I was seen in sclera (S).

Table 1 Concentrations of Hyp, Hyl, and Pro (nmol/mg defatted dried tissue) are given as mean (and range)

	Hyp	Hyl	Pro
Trabecular meshwork	390 (300–500)	37 (26–49)	610 (540–690)
Lamina cribrosa	230 (180–270)	21 (14–27)	470 (400–520)
Optic nerve	340 (300–390)	25 (20–28)	515 (440–580)
Sclera	610 (590–650)	44 (37–50)	850 (820–870)

Table 2 Hyp/Hyl ratios

	Lamina cribrosa	Trabecular meshwork	Optic nerve	Sclera
Sample eyes I a	13.0	11.4	14.7	14.8
b	11.7	13.7	15.4	16.1
II a	9.4	9.6	11.6	11.9
b	9.4	8.4	13.3	12.6

Four eyes from two persons. I and II.

work, though the Hyp concentration was about 50% higher in the sclera. The mean Hyp to Hyl ratio was 13.8 in the sclera and 13.8 in the optic nerve, which was significantly higher than in the two other tissues. The ratio of Hyp to Hyl was equal to that in the lamina cribrosa (10.9) and the trabecular meshwork (10.8). Fig. 4 shows the distribution of the individual results.

Discussion

The immunohistochemical findings showed the presence of collagen types I, III, and IV in the lamina cribrosa and in the trabecular meshwork. However, the staining of the type I collagen in the trabecular meshwork was weak. In a previous similar study² only type IV was detected in the trabecular meshwork. However, biochemical evidence³ suggested that type I is also present, as amino acid ratios similar to those of the dermis, which is rich in type I collagen, were obtained for the trabecular meshwork. The collagen

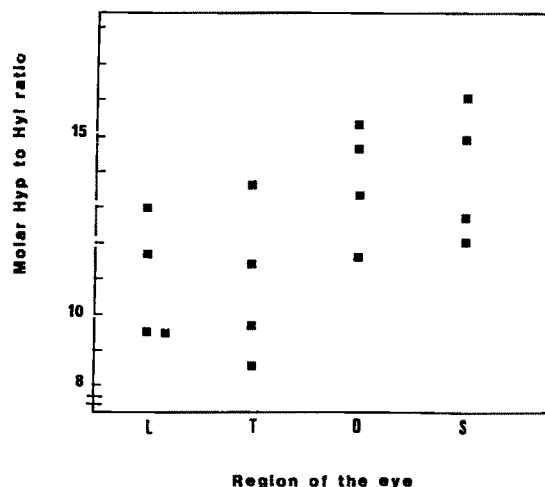


Fig. 4 The molar ratio of hydroxyproline (Hyp) to hydroxylysine (Hyl) was determined in samples of lamina cribrosa (L), trabecular meshwork (T), optic nerve (O), and sclera (S) from four eyes.

type distribution found in the lamina cribrosa is in agreement with earlier immunohistochemical work by Konomi *et al.*⁴

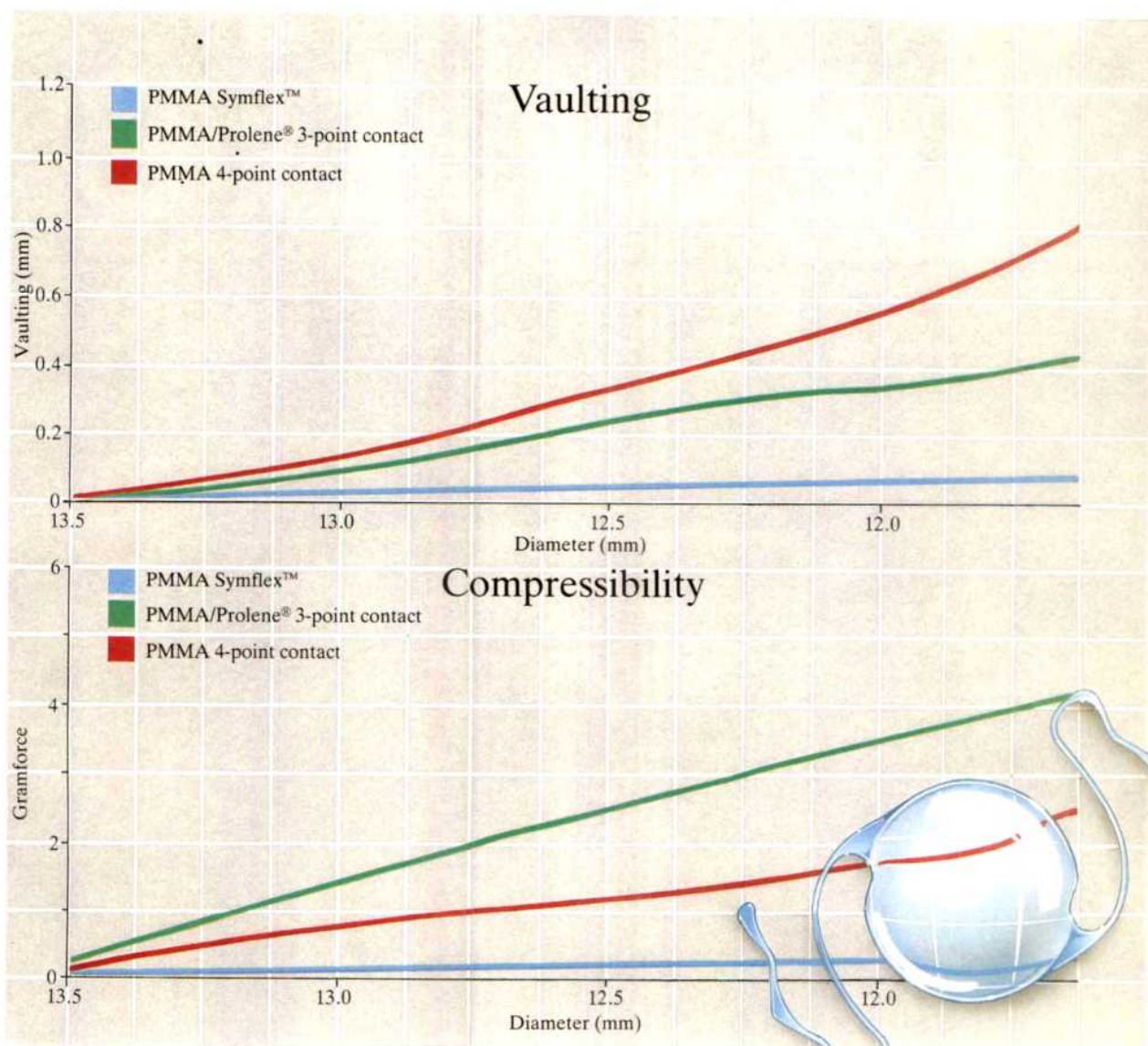
The Hyp to Hyl ratio of a tissue depends on the relative distribution of the molecular types of collagen, on the degree of cross linking, and on possible defects in the amino acid sequence. A relatively increased content of basement membranes causes a decrease in the Hyp to Hyl ratio because of a high content of Hyl in type IV collagen.⁵ This may explain the low Hyp to Hyl ratio and relatively high concentrations of Hyl in the lamina cribrosa and the trabecular meshwork as compared with the sclera and the optic nerve.

The similarity of the collagen type distribution between the trabecular meshwork and the lamina cribrosa suggested by the immunohistochemical findings is in agreement with the similarity in the Hyp to Hyl ratio, which indicates a resemblance in collagen composition of these structures. The results of the present study reveal the similarities between structures of particular interest in chronic open angle glaucoma. A common change of the supporting elements in these tissues, as suggested in earlier reports,¹ is of interest and will encourage further studies of the mechanical properties of collagen as well as a more detailed analysis of the collagen types present in normal and glaucomatous eyes.

The authors thank Mr Ole Christensen, Mrs Berith Spångberg, and Mrs Margareta Oskarsson for skilfull technical assistance, and Dr Peter Biberfeld for valuable advice. The study has been sponsored by the Crownprincess Margareta's Working Fund.

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Silicone oil removal. I. The effect on the complications of silicone oil

A G CASSWELL AND Z J GREGOR

From Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY The results of a retrospective study of the effects of silicone oil removal from 85 eyes in 85 patients are reported. Pars plana vitrectomy and fluid/silicone oil exchange had been undertaken for retinal detachments associated with giant retinal tears or with proliferative vitreoretinopathy in all cases. Clinically significant cataract developed in 60% of lenses that were clear at the time of oil removal, and 85% of pre-existing lens opacities progressed. Removal of oil from 19 eyes with uncontrollable glaucoma was combined with drainage surgery in 14 eyes. Postoperatively the intraocular pressure was controlled in 13. Corneal decompensation either improved or was unchanged in eight out of nine patients after silicone oil removal, and three patients had penetrating keratoplasty and maintained a clear corneal graft. Patients who did not have glaucoma or keratopathy at the time of silicone oil removal did not develop these complications.

Silicone oil has been used in the treatment of complex retinal detachments for many years.¹ However, many authors have reported postoperative anterior segment complications, such as cataract, glaucoma, and keratopathy even after successful reattachment of the retina.²⁻⁶ The possibility of a toxic effect of silicone oil on the retina remains controversial.⁷⁻¹¹

When silicone oil has been used in conjunction with vitrectomy, it can subsequently be easily removed via the pars plana in phakic eyes or via the limbus in aphakic eyes. It has been suggested that many complications may be prevented or their progression arrested when the silicone oil is removed a few weeks or months after surgery,^{12,13} but there are few reports detailing the effects of removing it either as a prophylactic measure or as part of the management of established complications.¹¹⁻¹⁶

The purpose of this study was to assess the effects of silicone oil removal on the anterior segment complications associated with its use. Perioperative and postoperative complications associated with silicone oil removal are reported in a separate communication.¹⁷

Patients and methods

The hospital records of 92 consecutive patients who

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had undergone silicone oil removal were reviewed. All patients, under the care of five vitreoretinal surgeons at Moorfields Eye Hospital, presented with retinal detachments associated with giant retinal tears or proliferative vitreoretinopathy and were treated by vitrectomy and fluid/silicone oil exchange. Patients with giant retinal tears and proliferative retinopathy were chosen because they represent the commonest indication for the use of silicone oil at this hospital. Patients underwent pars plana vitrectomy combined with epiretinal membrane dissection where appropriate and cryotherapy with scleral buckling as previously described.^{13,18,19}

Many patients, particularly those with proliferative vitreoretinopathy, had undergone multiple surgical procedures before silicone oil injection. After silicone oil exchange, but prior to its removal, further procedures were carried out in 25 patients. Supplementary photocoagulation of the peripheral retina was undertaken in eight, additional cryotherapy in two, and cryotherapy with scleral buckling in six. Epiretinal membrane dissection and silicone oil 'top-up' was required in four. One patient required the insertion of an anterior chamber drainage tube for intractable glaucoma. Anterior chamber paracentesis was performed in four aphakic patients in whom oil completely filled the anterior chamber, giving rise to markedly raised intraocular pressure.

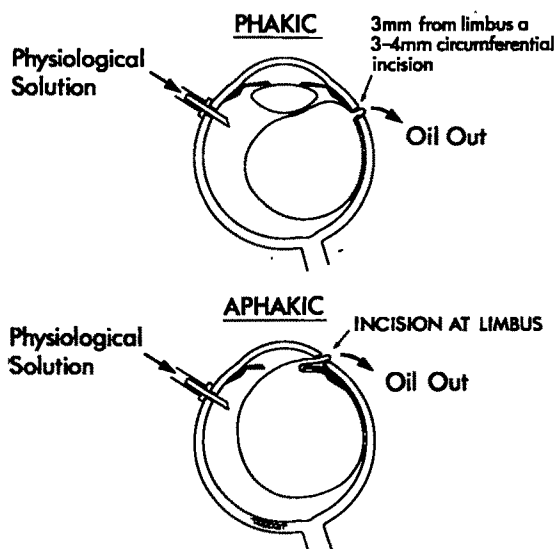


Fig. 1 Method of removal of silicone oil.

Many patients underwent silicone oil removal within one to three months to prevent the progression of lens opacities or development of glaucoma and keratopathy. Patients with uncontrollable glaucoma or keratopathy underwent silicone oil removal as part of the management of these complications.

Cataract was defined as progressive lens opacities documented on serial clinical examination. The presence of cataract alone was not an indication for removal of the silicone oil. Glaucoma was defined as intraocular pressure persistently greater than 30 mmHg on full medical treatment. Keratopathy ranged from corneal epithelial oedema at its earliest stage to stromal oedema, band keratopathy, and/or stromal thinning in more advanced cases.

The technique of silicone oil removal was that described by Leaver and Lean¹⁹ (Fig. 1). In some patients oil removal was combined with other procedures including lensectomy, trabeculectomy, aqueous drainage tube, or penetrating keratoplasty. Additional cryotherapy, scleral buckling, and/or epiretinal membrane dissection was undertaken at the time of oil removal if there appeared to be peripheral retinal detachment or persistent epiretinal traction.

Fundi were examined by indirect ophthalmoscopy at the end of the procedure in order to establish that the retina remained attached and that no large silicone oil bubbles remained in the vitreous cavity. A subconjunctival injection of antibiotics and steroids was given in each case.

Those patients with secondary glaucoma underwent removal of silicone oil when the intraocular

pressure became uncontrollable medically. If extensive synechiae at the peripheral anterior chamber angle were present, silicone oil removal was combined with a trabeculectomy or insertion of an anterior chamber drainage tube.

Patients with keratopathy underwent removal of silicone oil when corneal oedema had progressed to the extent of causing marked reduction of visual acuity.

Results

Of the 92 hospital records reviewed seven were excluded because of insufficient documentation. Of the remaining 85 eyes 59 had giant retinal tears, and 26 patients had proliferative vitreoretinopathy (PVR); these included five patients with PVR who had previously had penetrating trauma.

The duration of follow-up after removal of silicone oil ranged from three to 60 months (mean 18 months).

CATARACT

The effect of removing silicone oil on the lens was studied in patients who were phakic at the time of oil removal and had at least six months' follow-up postoperatively. Twenty eight eyes were already aphakic when the oil was injected, and six underwent lens extraction at the time of oil removal. Of the 51 eyes which remained phakic after oil removal 16 developed retinal redetachment and were excluded. A further three patients were excluded with a follow-up of less than six months, leaving 32 for analysis (Table 1). Eleven had clear lenses at the time of oil removal, and, of these, five remained clear at six months and six developed lens opacities. Twenty one already had lens opacities at the time of oil removal, and in 18 the lens opacities increased. This last group included five with lens opacities limited to early vesicular subcapsular opacities which cleared completely immediately after oil removal but recurred and progressed in each case after several weeks. Seven patients underwent cataract extraction during the period of follow-up.

Table 1 Lens clarity following silicone oil removal in patients with attached retinæ

	Total eyes	Unchanged		Increasing lens opacities	
		No. of eyes	Oil in situ (weeks)	No. of eyes	Oil in situ (weeks)
Clear	11	5	5-6	6	6-3
Opacities	21	3	6-3	18	10-6

Minimum follow-up six months.

The relationship between the length of time that the oil was in situ and the development of lens opacities is shown in Table 1. The mean length of time that the oil was in situ in eyes in which the lenses remained clear was 5.6 weeks, whereas in those which subsequently developed opacities it was 6.3 weeks. For patients whose pre-existing lens opacities did not progress the oil was in situ for a mean of 6.3 weeks, while for those who developed progressive changes the oil was in the eye for 10.6 weeks on average. No patient retained a clear lens if the oil remained in situ for more than 10 weeks.

Statistical analysis showed that eyes which developed lens opacities or in which lens opacities progressed had had silicone oil in situ for longer than those in which the lens status remained unchanged ($p=0.052$). Logistic regression analysis showed that the length of time that the oil was in situ had a significant effect on the probability of developing increasing lens opacities and that, when that was taken into account, the lens clarity at the time of silicone oil removal had little effect on the chance of progression.

GLAUCOMA

Nineteen patients underwent removal of silicone oil as part of the treatment of otherwise uncontrollable glaucoma. Although the follow-up ranged from three months to 36 months (mean 15 months), only two patients had a follow-up of less than one year. Fifteen patients were aphakic and four were phakic. Of the four phakic patients a globule of oil was present in the anterior chamber in three. The mean duration of oil tamonade was 20 weeks. The intraocular pressure was raised from the time of silicone oil injection in eight patients, and the remaining 11 patients developed glaucoma between six and 20 months.

After oil removal without an additional drainage procedure the intraocular pressure was controlled by medical treatment alone in three patients and remained uncontrolled in two (Table 2). One of the latter patients required a further injection of silicone oil after developing a retinal detachment. Of the nine patients who underwent trabeculectomy at or shortly

after oil removal the intraocular pressure was controlled in four, was moderately raised in one (24 mmHg), and in excess of 29 mmHg in four. Five patients were treated initially with the insertion of a silicone tube draining aqueous from the anterior chamber to a surrounding silicone explant. This was sufficient to control the intraocular pressure in two patients initially (one subsequently required cyclocryotherapy). In one patient the intraocular pressure remained moderately elevated (24 mmHg) and in two patients the intraocular pressure was uncontrolled (>30 mmHg).

Of the 66 patients without raised intraocular pressure at the time of oil removal (at 3–183 weeks with a mean of 15.0 weeks) five were found to have raised intraocular pressure following silicone oil removal. Of these patients one had congenital glaucoma, two developed raised pressure after a further injection of silicone oil for retinal redetachment and were controlled medically, and one developed mildly elevated intraocular pressure (24 mmHg) while the oil was in situ. Only one patient developed raised intraocular pressure following silicone oil removal; there was no other obvious predisposing cause and the intraocular pressure was controlled medically.

KERATOPATHY

Keratopathy was present in 11 eyes, nine aphakic and two phakic, and included five with glaucoma. The silicone oil was in situ for 16 to 240 weeks (mean 88 weeks) for patients with corneal problems alone and 16–60 weeks (mean 32 weeks) for patients with both glaucoma and keratopathy. A penetrating keratoplasty was required in two eyes at the time of silicone oil removal and in both patients the cornea remained clear at six months. In the nine remaining eyes there was an improvement of the corneal oedema in six. Four with coexistent glaucoma recovered a completely clear cornea and a gradual clearing of the central corneal oedema took place over several months in two. Corneal oedema was

Table 2 Results following oil removal in patients with uncontrolled glaucoma

Treatment	IOP controlled <21 mmHg	IOP 21–30 mmHg	IOP >30 mmHg or field loss
Medical (5)	3	0	2
Trabeculectomy (9)	4	1	4
Tube (5)	2	1	2
Total (19)	9	2	8

Mean follow-up of 15 months.

Table 3 Corneal clarity following oil removal

	Outcome at 3 months			
	Clear cornea	Less corneal oedema	Unchanged	Decompensated
Corneal oedema at removal (total 9)	4*	2†	2	1‡
Corneal graft at removal (total 2)	2			

* All had glaucoma and corneal oedema at oil removal.

† One had glaucoma.

‡ Corneal graft performed with good result.

unchanged in two eyes at six months following oil removal. Finally, one cornea became decompensated immediately after surgery and subsequently maintained a clear graft after penetrating keratoplasty (Table 3).

In the remaining 74 eyes in which there was no keratopathy at the time of oil removal no evidence of corneal decompensation occurred. The oil had remained in these eyes for 3–88 weeks (mean 11.8 weeks). The majority were phakic (55) while the oil was in situ, though 19 were aphakic and three phakic eyes had oil in the anterior chamber.

Discussion

The considerable controversy on the question of the complications of silicone oil has led to some retinal surgeons abandoning its use.²⁰ The principal complications in the anterior segment are cataract occurring in 49–100% of eyes,^{2,21} glaucoma in 11–33%,^{3,19} and keratopathy in 11–44%.^{3,4,22} Although inert gases have provided an alternative form of internal tamponade,²³ the use of silicone oil in combination with closed intraocular surgical techniques has been shown to be more successful in selected patients with PVR,¹⁴ and its use as a primary treatment for giant retinal tears achieves a high rate of retinal reattachment.¹³ In addition, after vitrectomy, silicone oil can be removed relatively easily and this may reduce the incidence of complications.¹²

The development of cataract in patients with complicated retinal detachments may be related to chronic retinal detachment or to multiple surgical procedures.^{24,25} We therefore excluded analysis of those patients who developed retinal redetachment. Our results demonstrate that opacities continue to develop even after removal of the oil in many patients. The longer the oil remained in the eye, the greater the risk of progressive lens opacities subsequent to its removal. No patient in this series failed to develop opacities if the oil was present for longer than 10 weeks. Gonvers reported a high rate of cataract formation after oil removal (78%)¹⁴ and our figures are in agreement with his.

We confirmed that glaucoma in patients following silicone oil injection occurs mostly in aphakic patients.²⁴ Some patients developed glaucoma in the first weeks after oil injection. These patients were almost all aphakic and had a broad or superior peripheral iridectomy. Since early glaucoma in aphakes with silicone oil appears to be commonly due to pupil block, it may be altogether prevented by an inferior peripheral iridectomy.²⁷ This has now become routine practice at this hospital but was not at the time that the patients in this series underwent surgery.

Roussat and Ruellan²¹ found that glaucoma in patients with silicone oil in situ was difficult to treat either medically or surgically, but successful filtering procedures after silicone oil removal in a small number of cases have been reported.^{14,15} Some aphakic patients responded simply to the removal of the oil, these usually having had high pressures from the time of oil injection. Of the patients who underwent removal of silicone oil for the treatment of glaucoma, with or without drainage surgery, most were controlled or had IOPs less than 30 mmHg postoperatively. With time several of the patients in this series have required further glaucoma surgery, such as the revision of the drainage tube or cyclocryotherapy, and it may be that the eventual number of patients whose intraocular pressures remain controlled in the long term would decrease.

Leaver *et al.*¹⁶ reported on three patients with keratopathy whose corneae showed evidence of clearing after oil removal, while Gonvers¹⁴ reported on four cases that developed corneal dystrophy after removal of silicone oil and required keratoplasty. Both Cairns and Anand¹⁵ and Beekhuis *et al.*²⁸ described patients whose clear corneae became decompensated after removal of silicone oil. In this series keratopathy was not a frequent indication for removal of silicone oil. Patients with keratopathy at the time of oil removal were mostly aphakic, and the silicone oil had remained in the eyes for a relatively long time (mean 56.2 weeks). The cornea cleared completely only in the patients who had corneal oedema associated with high intraocular pressure.

None of the eyes with clear corneae at the time of oil removal developed corneal decompensation after the oil was removed. Most were phakic and the corneal endothelium was protected from direct contact with silicone oil. In aphakic eyes or in phakic patients with oil in the anterior chamber the oil was in situ for a relatively short time.

In the animal model silicone oil in the anterior chamber appears to cause loss of endothelial cells, resulting in corneal oedema.^{29,30} However, most of our patients whose anterior chambers were filled with silicone oil retained remarkably clear corneae. It has been suggested that a large silicone oil bubble in the anterior chamber prevents access of aqueous to the stroma,^{29,30} and thus corneal oedema does not develop even in the presence of a reduced endothelial cell count; rather, in this situation corneal thinning may develop. Corneal oedema may increase when the oil is removed and aqueous gains access to the corneal stroma. On the other hand the clearing of the mild central oedema in some of our patients after oil removal might be explained by the spreading out of the residual endothelial cells to replace the damaged cells.³¹

All three patients who had a penetrating keratoplasty with removal of silicone oil maintained a clear graft. It has been reported that corneal grafts performed after oil removal have remained clear but were not as successful when the oil was left in situ.^{11,28}

In conclusion, we found that the occurrence of lens opacities or their progression is common after the removal of silicone oil, even after a short tamponade of a few weeks. Glaucoma and keratopathy can be prevented by removing the silicone. However, such complications are relatively infrequent in silicone filled eyes, and, if they do occur, they can be successfully treated once the silicone has been removed. Furthermore, the procedure of silicone oil removal carries a definite ocular morbidity,¹⁷ and it may be argued that this procedure is carried out only in eyes affected by glaucoma and keratopathy or in eyes at risk. Further studies are needed to identify such high risk patients.

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Silicone oil removal. II. Operative and postoperative complications

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SUMMARY A retrospective study of the effects of silicone oil removal was carried out on 85 patients who had undergone pars plana vitrectomy and silicone oil exchange for giant retinal tears or proliferative vitreoretinopathy. Silicone oil was removed either as part of the treatment of anterior segment complications such as glaucoma and keratopathy (25 patients) or in order to prevent these complications (60 patients). The major complications of the removal of silicone oil were retinal redetachment (25%), hypotony (16%), and expulsive haemorrhage (1%). The length of time that the oil remained in the eye and the presence of anterior segment complications did not appear to have an effect on the rate of retinal redetachment or hypotony.

Silicone oil has been used in the treatment of complex retinal detachments for many years and late complications have been reported by many authors.¹⁻⁵ Since silicone oil can now be readily removed from patients who have undergone pars plana vitrectomy, it has been suggested that temporary tamponade with silicone oil can prevent the development or progression of these complications.^{6,7} So far there have been few reports detailing the complications of the procedure of silicone oil removal.⁶⁻¹⁰

The purpose of this study is to report the peroperative and postoperative complications of removal of silicone oil in a large number of patients. The effects of silicone oil removal on the progression of pre-existing complications or prevention of potential complications associated with its use are reported in a separate communication.¹¹

Patients and methods

The patients and methods have been described in detail elsewhere.¹¹ Briefly, the records of 85 patients who had undergone silicone oil removal were reviewed. All patients had previously undergone pars plana vitrectomy and silicone oil injection for complicated retinal detachments associated with giant retinal tears (GRT) or proliferative vitreoretinopathy (PVR).

The decision to remove the silicone oil was made either to prevent anterior segment complications

(group I) or as part of the treatment of glaucoma or keratopathy (group II). In the majority of these patients the retina was attached prior to the procedure, though in some there was peripheral tractional retinal detachment.

The technique of the removal of silicone oil was as described by Leaver and Lean.¹² In some patients the oil was removed in combination with other procedures such as lensectomy, trabeculectomy, the insertion of an aqueous drainage tube, and penetrating keratoplasty. Cryotherapy, additional scleral buckling, and/or epiretinal membrane dissection was undertaken at the time of oil removal if there appeared to be a peripheral detachment or persistent epiretinal traction.

The fundi of patients were examined by indirect ophthalmoscopy at the end of the procedure in order to establish that the retina was attached. A subconjunctival injection of antibiotics and steroids was given in each case.

Results

Eighty-five eyes, 59 with GRTs and 26 with PVR underwent vitrectomy, epiretinal membrane dissection, and silicone oil-fluid exchange. These included five which had previously had penetrating trauma. Silicone oil was removed from 60 eyes to prevent late anterior segment complications (Group I) and from 25 as part of the treatment of glaucoma and keratopathy (Group II) (Table 1).

Table 1 *Reasons for silicone oil removal*

	Prevention of complications (group I)	Treatment of complications (group II)		
		Glaucoma	Corneal	Total
Giant retinal tears	45	10	4	59
Proliferative vitreoretinopathy	15	9	2	26
All patients	60	19	6	85

Table 2 *Average time the oil remained in situ (weeks)*

	Group I	Group II		Total
		Glaucoma	Keratopathy	
Giant retinal tears	9.3 (3-56)	14.7 (3-52)	51.5 (16-130)	13.3 (3-130)
Proliferative vitreoretinopathy	7.6 (3-16)	26.3 (6-60)	125.0 (68-182)	23.1 (3-182)
Total	9.1 (3-56)	20.2 (3-60)	76.0 (16-182)	16.3 (3-182)

Range shown in parentheses.

In group I the oil was removed after being in situ for three to 20 weeks (mean 9.1 weeks). The group II patients who developed glaucoma had oil in situ for three to 60 weeks (mean 20.2 weeks) and patients with keratopathy between 16 and 160 weeks (mean 76.0 weeks) (Table 2). The duration of oil tamponade was similar for GRTs and PVR.

Oil removal was combined with lensectomy (two patients), trabeculectomy (eight patients), the insertion of an aqueous drainage tube (four patients), and penetrating keratoplasty (two patients). Cryotherapy and additional scleral buckling were undertaken in four patients who had peripheral detachment or areas of residual vitreoretinal traction. Epiretinal membrane dissection was necessary in two patients. Cryotherapy alone was combined with oil removal in a further 11 patients (Table 3).

Of the 85 patients who underwent silicone oil removal one developed a peroperative expulsive haemorrhage. This patient had a giant retinal tear three years after intracapsular cataract extraction.

Table 3 *Additional procedures at silicone oil removal*

Procedure	Patients
Lensectomy	2
Trabeculectomy	8
Drainage tube	4
Penetrating keratoplasty	2
Epiretinal membrane peeling	2
Cryotherapy with additional scleral buckling	4
Cryotherapy alone	11

Following pars plana vitrectomy, injection of silicone oil, and 360° cryotherapy the retina became reattached. Four weeks after injection, removal of silicone oil was complicated by an expulsive haemorrhage, and the postoperative vision was reduced to perception of light.

Thin diffuse vitreous haemorrhage was a frequent finding immediately following oil removal, but this cleared in all but four patients between two and six days. In these four patients the haemorrhage cleared slowly over a period of several weeks.

Postoperative intraocular inflammation was mild in all cases and settled with the use of topical steroid treatment.

Following silicone oil removal 14 eyes (16%) had an intraocular pressures of less than 10 mmHg, including three eyes with intraocular pressures less than 6 mmHg. One of these three patients had had prior glaucoma surgery and one had had low intraocular pressure before oil removal; the third patient had had normal intraocular pressure prior to the removal of oil but subsequently developed marked hypotony with vision reduced to perception of light. The remaining patients had normal intraocular pressures prior to oil removal. Low intraocular pressure was present in 10 (16.9%) patients with GRTs and four (16%) patients with PVR. The oil was in situ for an average of 10 weeks.

Retinal redetachment occurred in 21 eyes (25%). Retinal redetachments occurred in 16 (26%) patients in group I and five (20%) in group II. Redetachments developed in 30% of patients with PVR and 22% with GRTs. Of the six eyes with areas of peripheral detachment that underwent scleral buckling at the time of oil removal only one subsequently became detached. Most retinal redetachments occurred soon after silicone oil removal; four were noted at the time of surgery, and a total of 12 became redetached within two weeks of surgery. Seventeen patients had redetached retinæ by three months (Fig. 1). The rate of redetachment appeared constant for different time intervals that the oil remained in the eye: 26% of

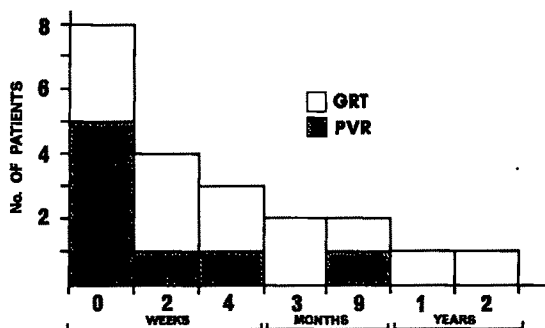


Table 4 *Duration that silicone oil remained in eyes that subsequently developed retinal detachments*

<i>Oil in situ (weeks)</i>	<i>Retinal detachment after removal</i>
3 to 5	5 (26%)
6 to 8	7 (25%)
9 to 11	4 (19%)
12 or more	5 (24%)

Table 5 *Outcome of patients with retinal redetachments following oil removal*

		<i>Reattached</i>	<i>Detached</i>
Conventional surgery	(7)	6	1
Gas	(3)	3	
Silicone oil	(7)*	6	1
No further surgery	(4)		4
Total	(21)	15	6

*One patient failed with gas and the retina became reattached after further injection of silicone oil.

Table 6 *Causes of loss of vision (hand movements or worse)*

	<i>Group I</i>	<i>Group II</i>
Retinal detachment	3	2
Expulsive haemorrhage	1	0
Hypotony	1	0
Cataract	1	0
Glaucoma	0	4

those with oil in for 3–5 weeks, 26% 6 to 8 weeks, 33% for 9 to 12 weeks, and 17% for more than 12 weeks (Table 4).

The anatomical outcome in patients who developed retinal redetachments following silicone oil removal is shown in Table 5. No further surgery was carried out in four patients. The retina was successfully reattached in 15 of 17 eyes in which further surgery was carried out. Scleral buckling and cryotherapy with or without SF₆-air mixture tamponade was successful in nine of 11. A total of seven patients underwent further exchange of silicone oil; in six the retina became reattached and one case failed.

Twelve patients (14.1%) lost formed vision (reduced to hand movements or less) during the period of follow-up. These included six (10%) patients in group I and six (24%) in group II. The cause of visual failure in group I were persistent retinal detachment (three patients), expulsive haemorrhage (one patient), hypotony (one patient), and cataract (one patient). In group II patients lost vision as a result of retinal redetachment (two patients) and glaucoma (four patients) (Table 6).

Visual loss occurred in seven (12%) patients with GRTs and five (19%) patients with PVR.

Discussion

The anterior segment complications of silicone oil injection are well recognised.^{1-3 13 14} In an attempt to avoid these complications the silicone oil may be removed at an early stage. Our figures suggest that the complication rate for the procedure is high: the major complications were retinal redetachment (25%), hypotony (16%), and expulsive haemorrhage (1%).

Expulsive haemorrhage causing marked loss of vision is a rare complication following intraocular surgery. Cairns and Anand² reported an expulsive haemorrhage on opening the silicone filled eye of a patient with glaucoma. Taylor reported expulsive haemorrhage in 0.2% of patients undergoing cataract surgery¹⁵ and identified risk factors such as high myopia, glaucoma, diabetes, atherosclerosis, and possibly general anaesthesia. The patient who suffered this complication in this series had no such risk factors, and cryotherapy was not performed at the time of oil removal.

The development of choroidal detachments with marked hypotony associated with severe loss of vision was a rare complication in this series, affecting only one patient. The retina remained attached but the vision was reduced to the level of hand movements. Gonvers⁷ found that six patients (5.8%) developed marked hypotony with vision reduced to perception of light after oil removal; the visual acuity recovered only when the oil was reinjected. He also reported that low intraocular pressures after silicone oil removal were relatively common; 20% had intraocular pressures of 1–5 mmHg and 55% had a pressure less than 11 mmHg. In our series hypotony was less common: 5% had an intraocular pressure of less than 1–5 mmHg and 17% less than 11 mmHg. Gonvers attributed the low intraocular pressures to cryotherapy of the anterior retina. Others have suggested that hypotony occurs in patients with persistent anterior retinal detachment or clefts in the anterior chamber angle,⁹ but we have not been able to confirm this.

There was a surprisingly high rate of redetachment of the retina following oil removal in this series. The rate was slightly higher for PVR than GRTs, though this was not statistically significant, and was comparable for patients of groups I and II and for different intervals that the oil remained in the eye. There appeared to be a slight reduction in the retinal redetachment rate for patients who had oil in situ for longer than three months, but this was not statistically significant. An important factor in the develop-

ment of retinal redetachment is the continuing traction exerted by epiretinal membranes present in PVR. Patients in this series with PVR were not classified according to the Retina Society terminology,¹⁶ as many underwent surgery before its publication. A review of the preoperative and postoperative records and retinal drawings suggested these patients may have had residual epiretinal membranes even after extensive epiretinal membrane dissection at the time of surgery.

We assume that most patients with giant retinal tears are affected by epiretinal fibrocellular proliferation to some degree. Many have surgery at an early stage, and thus clinical PVR was less likely to develop, and perhaps their retinæ were less likely to detach after oil removal.

Retinal redetachment occurs in the early weeks following vitrectomy and silicone injection,^{17,18} so it would be expected that in some of the patients undergoing a very early removal of oil (after three to four weeks) the retina would have become redetached even if the oil had been left in situ. None of the patients in group II had a pre-existing retinal detachment posterior to the encircling element implying that patients with detectable detachments were not offered surgery. Since the oil had been in situ for many months and the maximum cellular proliferative process is believed to be active for only two or three months,¹⁹ some of our patients were perhaps already preselected as being less likely to develop subsequent membrane contraction and retinal redetachment. However, we have not demonstrated a convincing reduction in the redetachment rate after extended silicone oil tamponade. Redetachment rates of 13%⁷ and 33%¹⁷ with PVR and 28%⁸ with GRTs have been reported following silicone oil tamponade of six to eight weeks. Reported redetachment rates range from 34%¹⁸ to 0%¹⁴ when the oil remained in the eye for 5.5 to 6 months. Clearly different patient selection and surgical techniques preclude a direct comparison between these different series.

Zivojnovic *et al.*¹⁷ and McCuen *et al.*¹⁴ emphasised the importance of the role of repeated epiretinal dissection while the silicone oil was still in situ. Others consider that panretinal photocoagulation prior to oil removal is an important factor in preventing later detachment,¹⁹ but this technique was not sufficient to prevent a redetachment rate of 34% in another series.¹⁸

In this study sight threatening complications occurred in 27% of patients undergoing silicone oil removal. 13% suffered irreversible severe loss of vision, the final visual results being better for group I (10%) than for group II (25%). The difference may be explained by the different types of complications

in the two groups. Retinal redetachment was relatively common in group I, and many of these patients recovered vision with further surgery. Glaucoma was common in group II and caused irreversible loss of vision in those patients who remained refractory to control.

As a result of our findings we have modified our approach to the removal of silicone oil. Since silicone is used for difficult detachments, often in 'only eyes', we recommend that silicone oil should be removed only in carefully selected cases. Those patients with no significant residual vitreoretinal traction and those who are most likely to develop sight-threatening anterior segment complications remain the obvious candidates.

We are indebted to R K Blach, R J Cooling, P K Leaver, and D V McCleod for allowing us to study their patients. We thank Mr P K Leaver for his comments on the manuscript and Mr P Clark for statistical assistance. This work was supported in part by the Friends of Moorfields, and A G Casswell holds a Friends of Moorfields Research Fellowship.

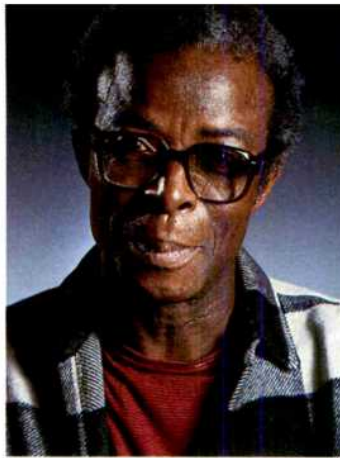
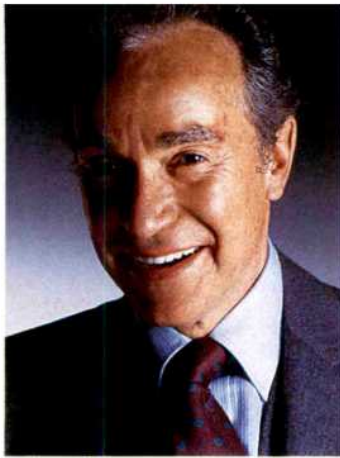
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Acute glaucoma following vitrectomy and silicone oil injection

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SUMMARY Three cases are described of acute glaucoma following vitrectomy and silicone oil injection in proliferative vitreous retinopathy. The first case developed silicone-induced pupillary block in a phakic eye. Cases 2 and 3 developed elevated pressure in aphakic eyes with deep anterior chambers. Cases 1 and 3 were treated by laser iridectomy. Case 2 was treated by removal of silicone. The pathogenesis and treatment of these problems are discussed.

In recent years there has been increasing success in the surgical treatment of severe cases of proliferative vitreous retinopathy (PVR) by a combination of vitrectomy and silicone oil injection.¹⁻³ Attention has recently been drawn to the risk of aphakic pupillary block glaucoma.⁴ The possibility of direct block of the trabeculum has also been proposed.⁵

We present three cases of acute glaucoma in phakic and aphakic eyes following silicone oil injection (1000 cs). The silicone itself was directly implicated in the pressure elevation. These cases demonstrate the various ways that silicone oil can disrupt aqueous humour dynamics in the anterior chamber.

Case reports

CASE 1

A 49-year-old man was referred to us for vitrectomy for severe PVR in the right eye. Ten months earlier he had undergone a buckling procedure for a large retinal hole. The retina was initially attached but later became detached again and the vitreous became organised. The left eye had undergone focal laser treatment for a retinal hole. At our initial examination the visual acuity was RE hand motion and LE 6/9. Intraocular pressure was 15 mmHg in both eyes and the angles were wide open on gonioscopy. The lenses were clear. On 18 June 1985 he underwent pars plana vitrectomy, membranectomy, and silicone oil injection with placement of an encircling band. During the procedure a small amount of silicone was noted to enter the anterior chamber, possibly owing

to a small zonulysis. The following day the anterior chamber was flat peripherally. The pupil was mid-dilated, with silicone bulging through, forming a shallow chamber centrally. The posterior chamber was very deep (about 2 mm) and completely filled with silicone (Fig. 1). The IOP was 35 mmHg and the angle was closed.

A YAG laser iridotomy was performed in the mid-periphery at the 3 o'clock position with immediate and dramatic deepening of the entire anterior chamber. The IOP dropped to 25 mmHg and later to 14 mmHg. The angle opened completely. A bulge of silicone remained in the pupil and the retina was attached. Five months after the silicone oil injection the lens became cataractous and he underwent an uneventful extracapsular cataract extraction with posterior chamber intraocular lens. Eleven months after the initial procedure the vision was 6/90, the retina was attached, and the intraocular pressure remained in the normal range without treatment.

CASE 2

A 57-year-old woman had undergone two retinal buckling procedures in her left eye. She was aphakic and highly myopic in both eyes and suffered from diabetes mellitus. On 3 March 1985 she underwent pars plana vitrectomy with silicone oil injection because of a severe PVR of the left eye.

Postoperatively the anterior chamber was filled with silicone but the IOP was normal. Two months postoperatively she presented with severe pain in the operated eye. The IOP was 64 mmHg, and the anterior chamber was deep and filled with silicone. The pupil was dilated, and angle structures could not

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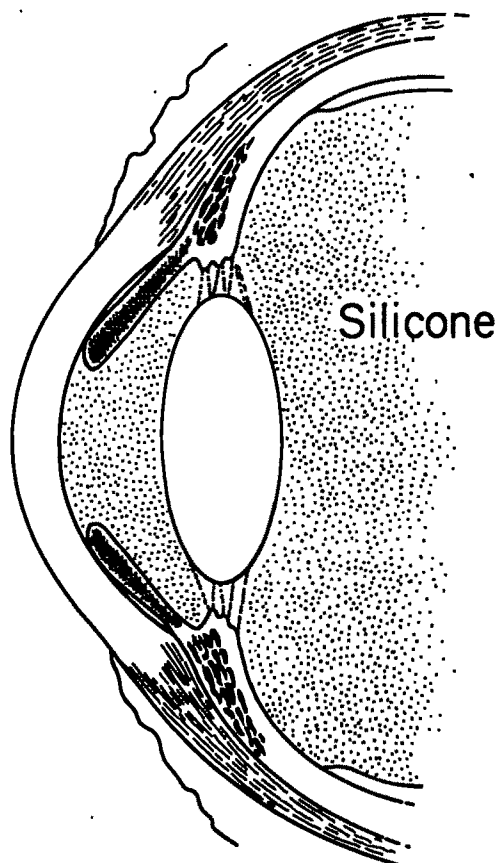


Fig. 1 Case 1, one day after operation. Note the silicone filling the posterior chamber and the extreme anterior displacement of the iris.

be seen. Conservative measures were unsuccessful in lowering the pressure, and she then underwent a partial drainage of the silicone via a limbal paracentesis. The IOP dropped to 8 mmHg. One month later, she again presented with an IOP of 64 mmHg and silicone oil filling the anterior chamber. Treatment was conservative and included lying prone.

The IOP dropped to 12 mmHg, and the silicone oil remained posterior to the iris. One year later the retina remained attached and the IOP was controlled with timolol and acetazolamide.

CASE 3

A 68-year-old woman was referred to us after two unsuccessful retinal buckling procedures in her left eye. At the initial examination her acuity was RE 5/7.5 and LE counting fingers. The IOP was RE 18 mmHg, LE 10 mmHg. The left eye had severe PVR and a vitreous haemorrhage. On 24 June 1984 she underwent a pars plana vitrectomy with silicone oil

injection. On 26 February 1985 she underwent intracapsular cataract extraction via a limbal incision with membranectomy and repeat silicone injection because of progressive traction detachment. The retina was reattached and her vision slowly improved to 6/30. In March 1985 the IOP began to rise and responded initially to medical therapy. The pressure became refractory to treatment and was as high as 42 mmHg. On 4 July under timolol and acetazolamide the IOP was RE 17 mmHg and LE 28 mmHg. The anterior chamber was deep and entirely filled by silicone. Gonioscopy revealed peripheral anterior synechiae in the superior quadrant and an angle open to the scleral spur over the remaining 270°. The cup/disc ratio was OD 0.2–0.3 and OS 0.7. A YAG q-switched laser iridotomy was performed at the 5 o'clock position. Thirty minutes later only a bulge of silicone was seen through the pupil and the remainder of the chamber was filled with aqueous. The appearance of the angle did not change, but the IOP was again amenable to medical therapy. Ten months after the laser iridectomy her vision was 6/60 and the IOP 19–24 mmHg under treatment with timolol and acetazolamide.

Discussion

Silicone oil is highly viscous and has a specific gravity less than water. The use of silicone has been shown to be effective in the treatment of PVR and sealing of retinal holes.¹⁻³ These same properties constitute a danger to aqueous humour dynamics in the anterior segment. As Ando⁴ has described in aphakic eyes, pupillary block can occur when the viscous silicone obstructs the pupil and an iridectomy, which is typically superiorly located. The problem will be alleviated by an iridectomy (surgical or laser) that is in the lower quadrant. The silicone, being lighter than water, rises in the intraocular space and obstructs the upper iridectomy. A small amount of fluid always remains in the inferior vitreous space.

Our case 1 developed a similar problem but in a phakic eye. To our knowledge this has not been previously described. During surgery there was a small zonulysis that allowed access of the silicone to the anterior chamber. Postoperatively this anterior flow of silicone apparently led to pupillary block. The striking anatomical feature of this case was the extremely deep posterior chamber and the almost flat anterior chamber, which made the treatment more difficult. The case bears some resemblance to the 'anterior pupillary block' syndrome described by Lazar,⁶ where the impediment to normal aqueous flow was an iridocorneal adhesion. If silicone oil is noted in the anterior chamber during surgery in the

phakic eye, it is recommended that a 6 o'clock iridectomy be performed as soon as possible.

In cases 2 and 3 the IOP rose in aphakic eyes with open angles on gonioscopy and deep chambers filled with silicone. It seemed that the silicone was blocking the trabecular meshwork by direct tamponade and that the best treatment would be to extract some of the silicone. This of course revives the risk of retinal detachment. Furthermore, as seen in case 2, this method of treatment may not be entirely effective. After extraction more silicone may flow forwards and trigger the same cycle of pressure elevation.

The true aetiology of pressure elevation in these two cases was a combination of pupillary block and direct obstruction.

Even when maximal amounts of silicone are injected, a small amount of fluid remains inferiorly as described above. As aqueous is produced, this pocket enlarges and pushes the silicone further and

further through the pupil until the entire anterior chamber and pupillary space is filled (Fig. 2). No aqueous can now reach the anterior chamber, and the pressure rises precipitously. The lower iridectomy allows at least a portion of the fluid to flow forward and find a level. Simultaneously some of the silicone flows posteriorly through the pupil (Fig. 3). The pupillary block is bypassed by the iridectomy, and the posterior movement of the silicone alleviates the direct block of the trabecular meshwork.

In their series Leaver and Grey⁷ described pressure elevations in 15% (14/93) of their cases. In nine of 14 eyes this was associated with numerous fine globules of silicone in the superior angle. They did not describe any cases of pupillary block. Similarly Haut *et al.*⁸ noted elevated IOP in 23 of 200 cases of silicone injection, mostly in aphakes. Twelve cases were considered angle closure, but they did not specify whether from peripheral anterior synechiae or

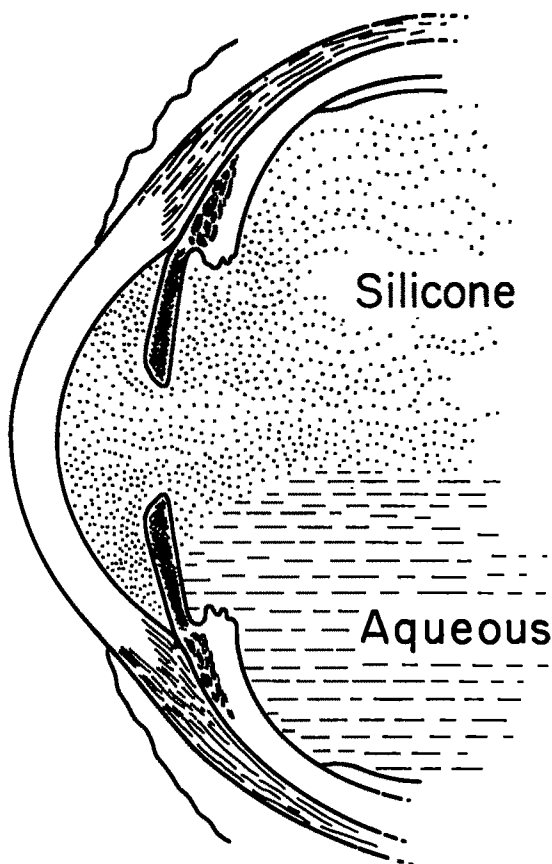


Fig. 2 Aqueous has sunk to the lower vitreal space. The silicone oil completely fills the remaining vitreous and pupillary space and the entire anterior chamber. The aqueous has no access to the trabecular meshwork.

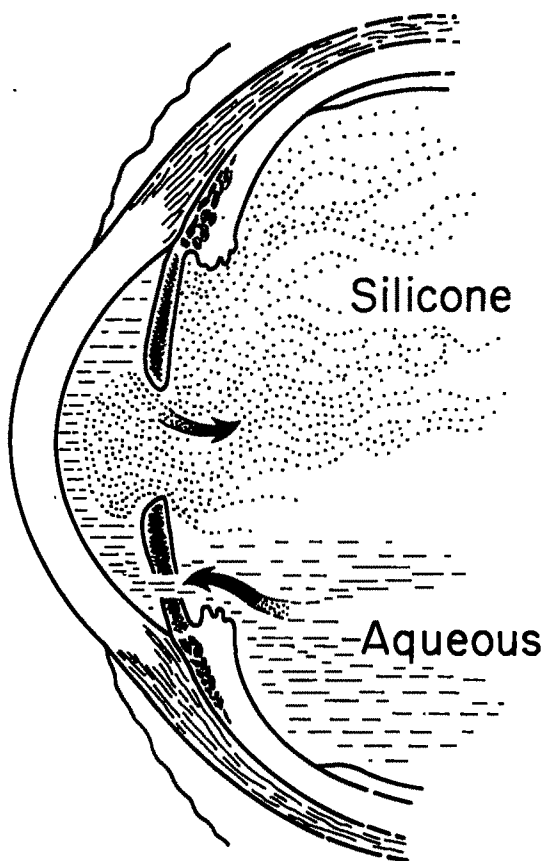


Fig. 3 After an inferior iridectomy the trapped aqueous flows anteriorly. This allows some silicone oil to flow posteriorly through the pupil. Both the pupillary block and the direct block of the trabeculum are alleviated.

pupillary block. In some cases emulsion bubbles were seen. Bubbles in a few of our silicone cases herein described.

Silicone oil carries a significant pupillary block glaucoma in aphakic eyes. Moreover, if the block component is not in a deep anterior chamber, a peripheral iridectomy can obviate the need for further procedures. This aspect of silicone oil has not been stressed in previous literature.

Pars plana vitrectomy is being performed with increasing success. Consequently the incidence of pupillary block glaucoma has decreased both the immediate and long-term periods.

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A method for fundus evaluation in children with oral fluorescein

BARUN KUMAR NAYAK AND SUPRIYO GHOSE

From the Paediatric Ophthalmology Service, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India

SUMMARY A procedure is described for the ophthalmoscopic examination of the fundus in children after 1% or 2% oral fluorescein ingestion without sedation or anaesthesia. No major complications or any allergic reactions were observed. In the ophthalmoscopically normal fundi of the five healthy children studied the fluorescence of the nerve head and retinal blood vessels could be visualised at 15 minutes, increasing at 30 minutes, and declining by 60 minutes. The possible problems of the technique are discussed.

Fluorescein angiography is undoubtedly a valuable investigative procedure in children, especially for the diagnosis of early papilloedema. For obvious reasons intravenous administration of fluorescein should be avoided if possible in these young patients. Peroral administration of the dye has been described,^{1,2} mostly in older patients. The present study is an attempt at standardising the procedure in infants and small children.

Materials and methods

The parents were explained about the purpose, procedure, and the possible side effects of the test. They were informed about the expected temporary yellowish discoloration of the skin, eyes, nails, and urine after administration of the dye and the known fallacies in certain laboratory estimations such as of blood sugar. The possibility of the older children complaining of yellowish vision was also explained. The investigation was undertaken only after we had obtained the informed consent of the parents.

The parents were instructed to keep the child fasting for two to three hours prior to reporting, the time depending on the age of the child, being shorter for younger children. The pupils were adequately dilated by alternate instillations of 5% or 10% phenylephrine and 2% homatropine drops every 15 minutes over one hour.

10% sodium fluorescein (Ophthalmic and Drugs Co., Bombay, India) used for human intravenous fluorescein angiography was diluted to 2% by adding

orange-flavoured soft drink. Acceptable palatability was ensured by pretasting it. This solution was then administered to the child at a dosage of 25 mg/kg body weight. No sedatives or anaesthetics were given. Prior antihistamines were not necessary.¹ The diluted dye was given as a fluid for the child to drink or suck from a feeding bottle—spoonfeeding was helpful in some smaller children. Depending on the total dosage of fluorescein dye required and the palatability of the mixture a 1% solution was also employed when necessary.

Initially five healthy children aged between 6 months and 5 years with no detectable fundus lesions were studied by this technique. Subsequently 23 more cases clinically diagnosed as pseudo-papilloedema and of 'suspected' and 'incipient' or 'early' papilloedema between the ages of 1 month and 10 years were investigated by oral fluorescein.³

During the fundus examination we concentrated on the posterior polar region with special reference to the optic nerve head and its fluorescence. The optic discs and major blood vessels were examined by the reduced and brighter illuminations of the Keeler binocular indirect ophthalmoscope with the standard blue Wratten filter supplied with it. The examination was undertaken initially, and later at 15, 30, and 60 minutes after ingestion of the dye. In eyes with disc oedema studied subsequently³ we focused our attention on detecting any late staining of the disc and peripapillary area. If the child co-operated, fundus photographs before and after oral fluorescein were also obtained when possible at the same time intervals.

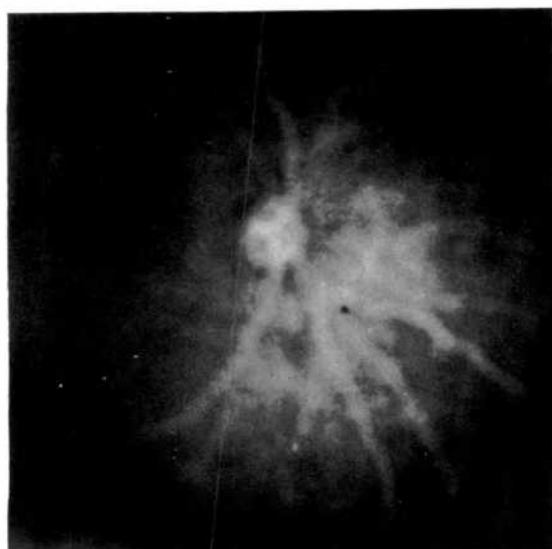


Fig. 1A

Fig. 1 The fluorescein fundus serial photographs at 30 and 60 minutes of the right eye in a normal child after 2% oral fluorescein. Note the easily visible fluorescence of the disc (more at the margins) and the large retinal blood vessels at 30 minutes (A), markedly declining at 60 minutes (B) with the dye localised mainly to the venous side of the circulation. The disc margins are well defined.



Fig. 1B

Results

The solutions of oral fluorescein prepared as above were found to be generally acceptable to the small children tested, though the odd case required a judicious amount of coercion for the total dosage to be administered.

No major complications were encountered, and no allergic reactions were observed. Two children (1½ years and 7 years) vomited the solution (2%) soon after ingestion. The former was known to have frequent seizures with vomiting, and the child did have a convulsive episode along with the vomiting; the general condition and systemic examinations were otherwise unremarkable.

In the five children initially examined with no known or detectable fundus lesions, initial funduscopy after oral fluorescein revealed a normal fundus and discs with faint though just detectable fluorescence either uniformly over the nerve head or localised to the disc margins. The disc margins were invariably sharp and well defined. The fluorescence of the nerve head was observable at 15 minutes, and was more prominent at 30 minutes (Fig. 1A), though it declined at the 60 minutes phase (Fig. 1B).

The faint degrees of fluorescence were much better detected with reduced levels of illumination.

After oral fluorescein the initial angioscopy of course did not reveal the dye in the retinal blood vessels. At 15 minutes the dye could be visualised, and at 30 minutes the dye was observed to be fairly evenly distributed in the retinal vessels (Fig. 1A). At 60 minutes the dye was less pronounced in the vessels, and was mainly localised to the venous side of the circulation (Fig. 1B).

Our results in the eyes subsequently investigated with clinical diagnoses of early papilloedema or pseudopapilloedema will be detailed later.¹

Discussion

Though oral fluorescein angiography has been recommended in certain types of cases,^{1,2} the problems and patience required in examining children by this test are obvious. Not the least of them is the difficulty in administering the drug. An acceptable vehicle may have to be found, and the container may vary from a feeding bottle to a spoon or a glass; even administering the liquid through a Ryle's tube may be considered as a possibility. The palatability of the mixture is obviously important, though an adequate concentration must be attained. The dye solution was administered on a virtually empty stomach to ensure better and quicker absorption.

We found that a dosage of 25 mg/kg body weight in 2% or 1% dilution was acceptable, safe, and effective in the children studied. One of the two who vomited may not have done so because of the dye administered, and in both these children the test could be

successfully performed after three days with 1% dye concentration. Though a higher dosage may probably be used, its possible side effects and toxicity in children are not yet clearly established.¹

Whatever may be the concentration of the dye administered orally, the 'bolus effect' of intravenous injection cannot be achieved, though it has been shown earlier that the 30 minutes serum levels after intravenous and oral administration are similar.¹ The concentration of fluorescein within the blood vessels, however, was sufficient to make them faintly visible angiographically by 15 minutes after ingestion. The vascular (and optic nerve head) demarcation was satisfactory by 30 minutes (Fig. 1A), and declined consistently in the normal fundi by 60 minutes (Fig. 1B).

The comfortable examination of the fundus in such young children even after intravenous fluorescein would demand a fairly prolonged anaesthesia, or at the best a repeat anaesthetic administered after 30 minutes. For most children requiring this investigation such an anaesthetic would surely be less desirable.

There are obvious problems in the satisfactory assessment without anaesthesia of the child's fundus after dye administered orally. A standard fundus fluorescein camera may be feasible for the older and more co-operative children. A suitable hand-held fundus camera may be employed with the child supine, but this again usually requires general anaesthesia. Photographic recording also has its own problems and sources of error.⁴ A possible alternative is fluorescein funduscopy with the recommended blue filter. Both direct⁴ and binocular indirect ophthalmoscopes may be useful, though we have

used the latter with a +14.0 D condensing imaging lens for optimum magnification and stereopsis.

The definition of the dye on funduscopy should theoretically be much sharper if a green barrier filter can be incorporated in the observation system. This should eliminate the practical problem of pseudo-fluorescence and assist a more sensitive and reliable detection of even the faintest level of fluorescence after oral administration of the dye. Till the incorporation of such a barrier filter is practicable, we would recommend using reduced levels of illumination. The optimum intensity of illumination would have to be standardised by the individual clinician on his available apparatus.

Oral fluorescein is hardly ideal for a detailed study of the retinal vasculature. Its main clinical uses remain the detection and localisation of 'late' fluorescence or 'leaks', as from the abnormally permeable blood vessels, macular lesions, and disc oedema. We have found our method of fluorescein funduscopy to be helpful, with emphasis on 'papilloscopy'. Our experiences with oral fluorescein as a diagnostic aid in suspected and incipient papilloedema will be discussed subsequently.³

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Role of oral fluorescein in the diagnosis of early papilloedema in children

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SUMMARY Nine eyes of suspected papilloedema, 21 with incipient papilloedema, and 16 with pseudopapilloedema in 23 children aged 1 month to 10 years were examined after oral fluorescein. In pseudopapilloedema the retinal vascular fluorescence and slight disc head fluorescence with sharp margins at 30 minutes markedly declined by 60 minutes. These features were similar to our earlier findings with oral fluorescein in the normal fundi of children. Of the 30 eyes with suspected or incipient papilloedema late disc and peripapillary 'staining', polar or diffuse was observed in 12, the 60 minutes fluorescence being more than at 30 minutes in nine and of equal in intensity in three. In these 12 'positive' eyes, and four more of the 18 'negative' eyes, the retinal vascular fluorescence at 60 minutes was significantly more than at 30 minutes. The problems of interpretation after oral fluorescein in the early diagnosis of papilloedema in children and the possible fallacies are discussed.

There are several conditions in children in which papilloedema is well known,¹⁻⁴ and its early diagnosis is vital in effectively monitoring the treatment and considering timely surgical intervention. In children, however, the early diagnosis of papilloedema is almost entirely dependent on objective features. The ophthalmoscopic diagnosis in 'suspected'² or even in 'incipient' or 'early'³ papilloedema may be difficult. Any one sign by itself may be unreliable, and the total picture in its entirety would have to be evaluated before arriving at a clinical opinion. Careful fundus examination, including red-free ophthalmoscopy,⁵ fundus photography, and repeated evaluations,⁶ may aid in the early diagnosis.²

Fluorescein angiography has always been considered to be valuable in the early detection of papilloedema.^{1,7,8} But the necessity of its conventional intravenous administration usually precludes its wider usage in small and often deformed children. The role of peroral administration of fluorescein dye (oral FA) is gaining importance.^{9,10} This paper details our experiences of oral fluorescein in children with special reference to the evaluation of its clinical applicability for the early diagnosis of papilloedema.

Material and methods

The procedure adopted by us for oral fluorescein in children has been detailed earlier.¹¹ The pattern obtained in a few healthy children with normal discs and no detectable fundus abnormality was described.

In the present study 15 children of one month to 10 years of age (Table 1) with the diagnosis of 'suspected' or 'incipient' papilloedema were studied. Of these 15 children 10 had hydrocephalus, three convulsive disorders, one a suspected intracranial space occupying lesion, and one a unilateral proptosis.

The fundus examination was routinely carried out after topical phenylephrine as an outpatient procedure, without sedatives or anaesthesia.² The details

Table 1 Age and sex distribution of the 23 children examined with oral fluorescein

Age	Number of cases	Male	Female
1 month to 11 months	11	9	2
1 year to 4 years	4	3	1
5 years to 10 years	8	4	4
Total	23	16	7

Table 2 *Disc findings after oral fluorescein in 30 eyes of suspected and early papilloedema in 15 children*

Fundus findings	Group	No. of eyes	Late disc staining after oral fluorescein			
			Negative	Positive		
				Polar	Diffuse	
Venous engorgement (VE) only	1	9 (5)*	9 (5)	—	—	
VE with blurring of poles	2	17 (9)*	9 (5)†	6 (4)†	2 (1)	
VE with diffuse blurring of disc margin	3	4 (2)	—	—	4 (2)	
Total		30 (15)	18 (10)	6 (4)	6 (3)	

Figures in parentheses denote number of children.

*One patient was observed to have different clinical findings in his two eyes.

†Another patient of group 2 showed polar staining in his right eye, but no staining could be detected in the left eye.

of the optic nerve head were noted, with special reference to the colour and margins of the disc, the physiological cup, blood vessels, venous pulsations (spontaneous or induced), venous engorgement, venous tortuosity, and the presence of any oedema, haemorrhage, exudates, and sheathing.² Cases of 'developed papilloedema' with obvious oedema with or without haemorrhages were excluded from this study.

The term 'incipient' or 'early' papilloedema³ was used to denote the disc picture before significant swelling could be detected. All these discs showed hyperaemia, shallowing or filling up of the cup, mild venous engorgement, and blurring of one or both of the upper and lower poles, or diffuse blurring of the disc margins. Twenty-one such eyes in 11 patients formed groups 2 and 3 in this study (Table 2).

When only venous engorgement was observed, without or with only minimal blurring of the disc margins, the disc was labelled 'suspected' papilloedema.² Nine such eyes in five children comprised group 1 of this study (Table 2). Except for the 1-month-old infant with unilateral proptosis whose discs showed a faint uniform pallor, all these eyes had hyperaemic discs in addition to the venous engorgement.

Sixteen eyes in eight more children below 10 years of age (Table 1) with a primary clinical diagnosis of pseudopapilloedema were similarly investigated by oral fluorescein. Though mild venous engorgement and hyperaemia were observed in all these eyes along with indistinct disc margins,⁷ the nerve fibre pattern at the margins could be discerned quite clearly on careful fundus examination, especially with red-free ophthalmoscopy.⁸ However, as suspected or early

papilloedema could not be ruled out clinically, they were also studied with oral fluorescein. Three of these children had convulsive disorders, two complained of persistent headache, two more were hypermetropic, and one was suffering from prolonged fever.

These 16 eyes clinically labelled as pseudo-papilloedema and the 30 eyes with suspected or early papilloedema were investigated after oral fluorescein. The optic discs and blood vessels in the posterior fundus were examined by the reduced and brighter illuminations of the Keeler binocular indirect ophthalmoscope (with the blue Wratten filter) initially, and again at 15, 30, and 60 minutes after dye ingestion.¹¹ The relative intensities of fluorescence, especially at 30 and 60 minutes, in the papillary and peripapillary areas and of the easily visible larger blood vessels were noted. Wherever possible, fundus photographs before and after oral fluorescein were obtained at these time intervals.

Results

The age and sex distribution of these 23 patients are depicted in Table 1.

In the 16 eyes with pseudopapilloedema, the slight fluorescence of the disc head observed by 30 minutes almost disappeared by 60 minutes (denoted negative) (Fig. 1).

For the 30 eyes of suspected or incipient papilloedema, the disc features in the various groups after oral fluorescein, with basic reference to the late papillary and peripapillary staining, are analysed in Table 2. The late staining was either diffuse, involving the entire disc margin and surrounding area (Fig. 2), or relatively localised to one or both poles of the disc and adjoining areas. The 60 minutes fluorescence was invariably more prominent than or equal to that observed by 30 minutes (denoted positive, Table 2, Fig. 2). In three eyes with polar staining the 60 minutes fluorescence was equal to the 30 minutes intensity.

All the cases positive on oral fluorescein turned out later to have radiographic/CT (computed tomography) evidence of raised intracranial pressure. Cases negative on oral fluorescein had no such evidence, except only one child with hydrocephalus, in whom CT later suggested raised pressure.

In all the 16 eyes with pseudopapilloedema the fluorescence of the retinal vessels at 60 minutes declined as compared with the 30 minutes intensity. However, of the 30 eyes with suspected or early papilloedema 12 with positive late disc staining, polar or diffuse (Table 2), showed fluorescence of the retinal vessels at 60 minutes significantly more than at 30 minutes (Fig. 2). This increased vascular fluoresc-



Fig. 1A

ence was also observed in four of the 18 negative eyes (Table 2) with no significant late disc staining.

Discussion

The fundus features used by us to differentiate clinically between pseudopapilloedema, suspected papilloedema, and incipient or early papilloedema were based on our own past experiences in such children⁷ and on published views.^{5,8,12}

The ophthalmoscopic diagnosis in the early stages may often prove difficult, especially in small children.

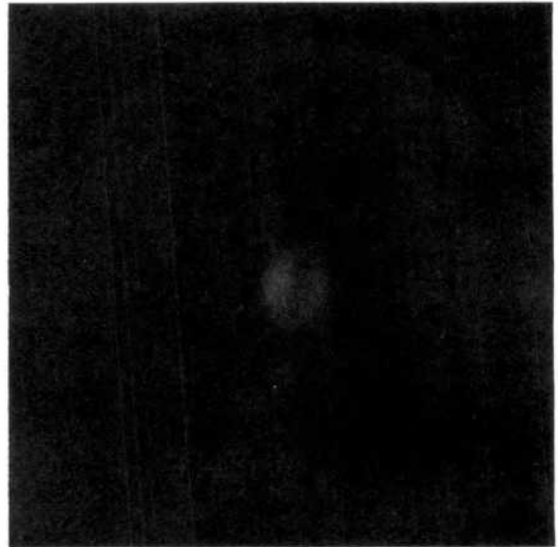


Fig. 1C

Fig. 1 The fluorescein fundus serial photographs after 2% oral fluorescein at 15, 30, and 60 minutes in the right eye of a child with pseudopapilloedema. Note the detectable diffuse fluorescence of the disc and large retinal blood vessels at 15 minutes (A), increasing at 30 minutes (B), and markedly declined at 60 minutes (C). The disc margins are well defined.

It is important to realise that the presence or absence of spontaneous or induced venous pulsations in itself does not decide the diagnosis.^{2,8} The importance of venous engorgement as a more definite and reliable indicator of early papilloedema is known.^{2,5,8} Slight

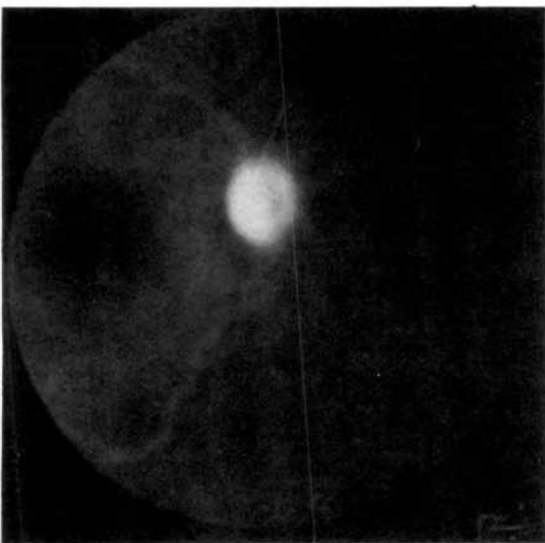


Fig. 1B

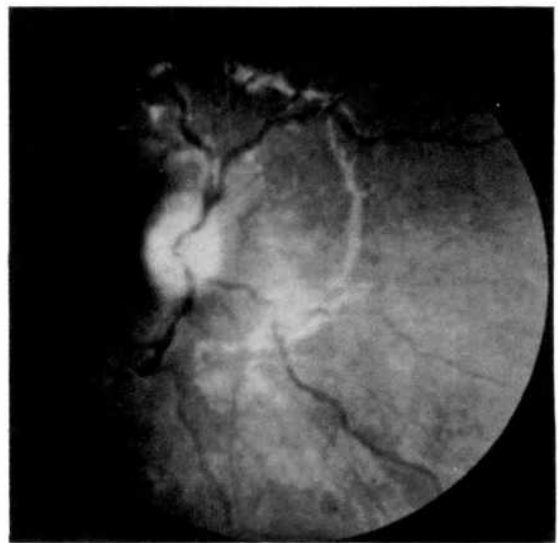


Fig. 2A

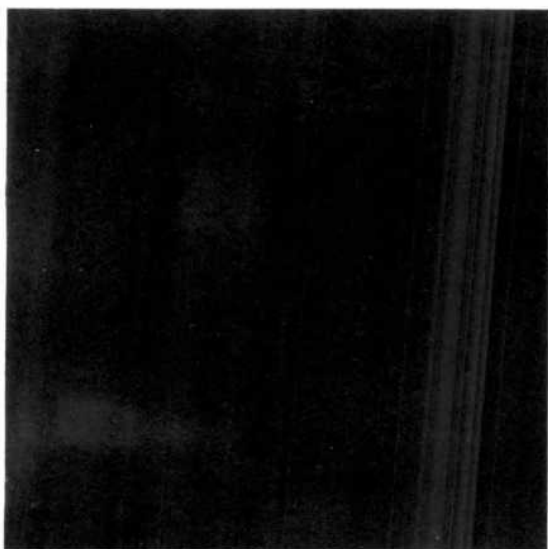


Fig. 2B

Fig. 2 The fundus (A) and fluorescein fundus serial photographs after 1% oral fluorescein at 15, 30, and 60 minutes in the left eye of a child with incipient papilloedema. Note the just detectable disc fluorescence at 15 minutes (B), and better visibility of diffuse disc and retinal vascular fluorescence at 30 minutes (C), increasing to a maximum at 60 minutes with peripapillary staining (D). The right eye at 60 minutes showed a similar picture (E).

blurring of the upper or lower poles or both has been in our experience a very suspicious feature, especially when an observable venous engorgement is coexistent, even if the other 'typical' features of 'early'

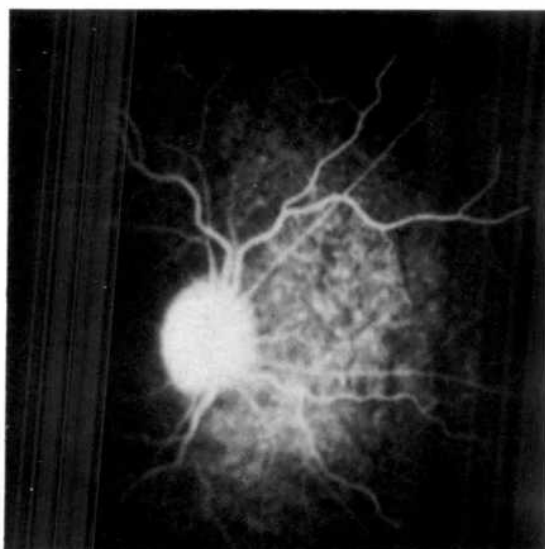


Fig. 2D

papilloedema' are absent; diffuse blurring of the disc margin (usually nasal more than temporal) strongly adds to the clinical suspicion.

In our study venous tortuosity was hardly evident in the earliest stages. Disc hyperaemia was observed in all the eyes, except in the one eye with unilateral proptosis of a 1-month-old infant, where the faint, uniform, bilateral disc pallor appeared to be within normal limits for the age of the child. Hyperaemia was also noted consistently in the discs with pseudo-papilloedema. Though the physiological cup was occasionally shallowed, a veil-like greying in this area

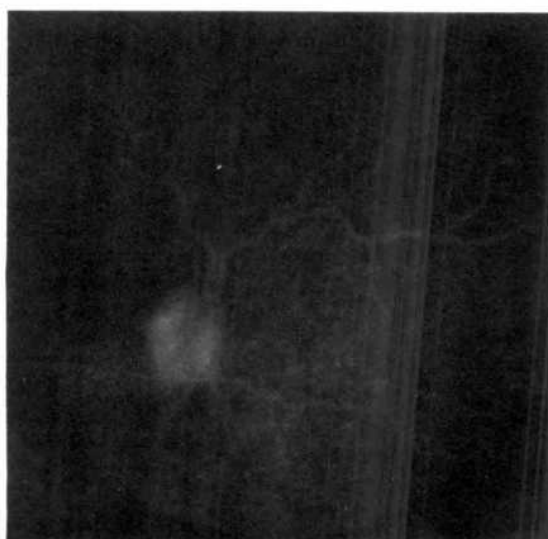


Fig. 2C



Fig. 2E

was seldom observed. However, disc hyperaemia and veiling of the tissue at the centre of the disc, though emphasised in the literature as important early signs,^{3,12} do not seem to be as significant as venous engorgement as very early indicators.

Though fluorescein angiography is well known in the differential diagnosis of pseudopapilloedema and papilloedema,⁷ and has also been considered useful in diagnosing early papilloedema,¹⁸ it has been reported earlier that this is not very satisfactory in the detection of the very early stages of disc oedema.⁵

In another series studied by intravenous fluorescein,¹³ in four out of 16 cases the fluorescein ophthalmoscopy was inconclusive for diagnosis of the papilloedema proved later, and the test in fact was declared negative. Though fluorescein ophthalmoscopy is usually valuable for the differentiation of papilloedema and pseudopapilloedema, even intravenous fluorescein in adults may give a negative result which does not exclude the possibility of papilloedema,¹³ and the method is not entirely reliable.¹³ Fluorescein angiography may fail to distinguish incipient papilloedema in all instances.⁵ Unfortunately no further data seem to be available to prove or disprove this. Hence the early detection of papilloedema by oral fluorescein in small children would obviously be even more problematical.

In our interpretation of the fundus pattern after oral fluorescein from the standpoint of the early diagnosis of papilloedema we were concerned with detecting late 'staining' of the disc and peripapillary areas. In the normal fundi of healthy children the observable fluorescence of the disc head at 30 minutes almost disappeared by 60 minutes.¹¹ In the six eyes found in the present study to show diffuse late staining (Table 2), the 60 minutes disc fluorescence was consistently more intense than that observed at the 30 minutes phase.

In the six more eyes with late staining relatively localised to one or both poles of the disc and the adjoining areas the 60 minutes fluorescence was either more prominent than or equal in intensity to that noted at 30 minutes. It is significant that the 60 minutes fluorescence was never less than the 30 minutes phase in these eyes. It is possible that in those three eyes with equivocal intensity at 30 and 60 minutes the investigative diagnosis should be interpreted as 'suspected positive', rather than just 'positive' as denoted in our analysis in Table 2. In this connection it is interesting that dye leakage in developing and developed papilloedema has also been noted to be more in the vertical disc axis.¹⁴

In our 16 eyes investigated with the clinical diagnosis of pseudopapilloedema it is significant that the pattern and decline of fluorescence after oral administration were virtually identical with that of

normal, with the disc margins appearing quite well defined at 30 minutes and no staining of the peripapillary area.

It must be remembered that fluorescein after administration, either orally or intravenously, becomes tagged to the plasma proteins and hence is detectable only as 'staining' or 'leaks' when it comes out of the circulation with the extravasated plasma,^{7,14} a state which appears clinically as concomitant disc swelling. Therefore, 'positive' interpretation of oral fluorescein in early papilloedema on the basis of late papillary staining is dependent only on the disrupted functional integrity of the retinal vascular barrier of the capillaries on the optic nerve head. This stage of pathognomonic staining of the nerve head after oral fluorescein is equivalent to the late phase of conventional intravenous fluorescein angiography. Hence it is quite probable that, in spite of a 'negative' result with fluorescein, it may angioscopically be indeed possible to miss the very earliest stages of papilloedema, which perhaps manifest only as venous engorgement without any detectable transudation of the intravascular fluid into the glial tissues of the disc head. Oral fluorescein with higher dye concentrations repeated over intervals and even intravenous fluorescein may have to be considered to rule out the earliest stages of impaired vascular permeability.

However, it is interesting that in all of the 12 eyes denoted 'positive', and in four of the 18 eyes declared 'negative' for disc staining (Table 2) the vascular fluorescence of the easily observable large retinal vessels at 60 minutes was significantly more than at 30 minutes, in contrast to normal eyes.¹¹ It is probable that the already existent venous stasis and stagnation of blood circulation⁶ are related to this failure of decline of fluorescence. This situation would be compatible with the initial venous engorgement as a very early indicator,² and yet not allow capillary permeability to be so significant on the disc head as to give rise to detectable late disc staining. Hence these four eyes denoted 'negative' in Table 2 should possibly be interpreted as 'suspected positive'.

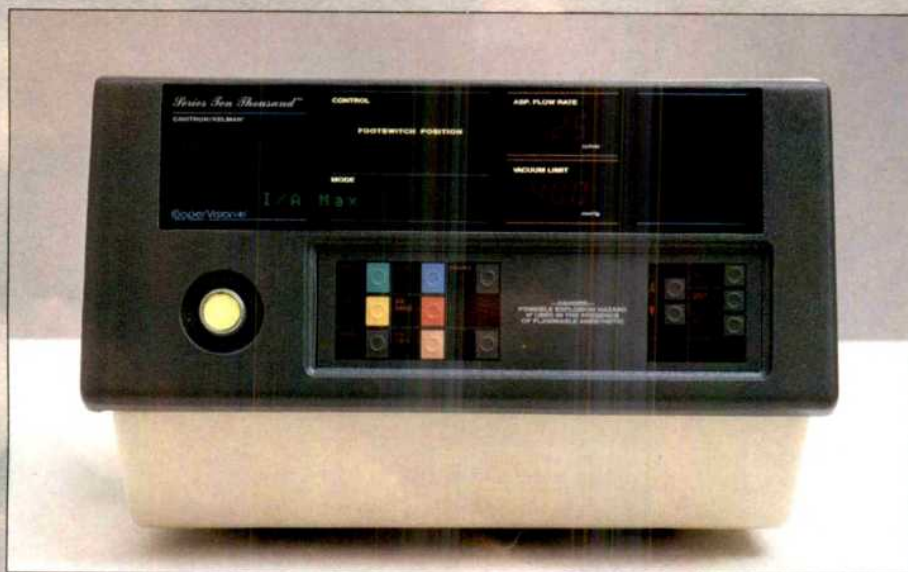
In an earlier series a few children had been examined by oral fluorescein angiography,⁹ though none of them was suspected of having papilloedema. Our admittedly short-term study is a preliminary attempt at the evaluation of this problem. A much larger and multicentred study would afford adequate clinical experience of the diagnostic criteria in children by oral fluorescein in this very difficult group of cases.

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An estimate of the size and shape of the human lens fibre in vivo

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SUMMARY The size and shape of the lens fibres were estimated by specular reflex photography. The fibres were measured in three separate regions. Peripheral fibres have a mean width of 10.2 μm , the central fibres 11.9 μm , and the central fibres with suture 15.8 μm . Measurements were made of the taper (becoming narrower towards the suture) and flare (becoming wider towards the suture). The peripheral fibres have a mean taper of 0.3 μm per 100 μm . The central fibres have a mean flare of 0.6 μm per 100 μm , and the central fibres with suture have a mean flare of 2.4 μm per 100 μm . These differences are highly significant ($p < 10^{-6}$). From these measurements the overall shape of the average lens fibre was estimated. This fibre tapers as it passes forward from the equator to the peripheral extent of the lens sutures and then flares increasingly as the junction with the lens suture is approached. A mean increase in peripheral lens fibre width with age at 0.028 μm per year was demonstrated. This is significant ($p = 0.042$). No difference in fibre width was found in diabetics and non-diabetics.

The lens fibres of the human eye run an elliptical course from their termination at a suture line anteriorly to their other termination at a suture line posteriorly. Their length has been estimated by examination of the lens in vitro at 8-10 mm by Salzmann,¹ and this figure has been widely quoted since.² This figure appears perfectly acceptable and cannot be confirmed in vivo. Kuszak *et al.*³ observed in vitro that the fibres are wider at their posterior ends than at their anterior ends. In-vivo observation by specular photography can give information on the lens fibre width and how this changes in various regions of the anterior part of the fibre only.

Vogt⁴ observed in vitro that the fibres tapered from the equator towards the peripheral extent of the lens sutures and then flared towards their insertions in the sutures. The electron microscope studies of Kuszak *et al.*³ showed no taper in the fibres of human lenses and that the fibre is flared in the proportion of 1:1.7 in its course from the equator to the suture.

The lens fibre width was estimated in vitro by Salzmann as 8-12 μm and there appear to have been no further estimates until the specular photographic studies of Laing and Bursell,⁵ who estimated the

width as 8 (SD 2) μm and Bron and Matsuda,⁶ whose estimate was 7.8 to 17.4 μm with a mean of 13.7 μm . Bron and Matsuda's figures are uncorrected for the corneal magnification and it is not stated whether Laing and Bursell's figures are corrected.

A variety of specular reflex images can be obtained from the anterior lens surface with the slit-lamp microscope or with the macro camera. The appearance depends on the angles of illumination and viewing and on the depth to which the camera or microscope is focused in the eye. The anterior corneal shagreen (Fig. 1) is easily demonstrated. The next appearance to be demonstrated is an arrangement of fine spots (Fig. 2) representing the lens epithelium. (A specular reflex study of the lens epithelium has been submitted for publication.) With the focus at a slightly deeper level, a pattern of fine parallel lines (Fig. 3) is seen, and these lines represent the borders between the lens fibres. The fibres are seen to be near parallel sided in the periphery (Fig. 4) and flaring markedly as a suture is approached (Fig. 5). This appearance is seen in exaggeration (Fig. 6) when the lens fibres are swollen by oedema in a newly acquired traumatic cataract.

The recognition that several types of cataract take their form from the organisation of the lens fibres⁷

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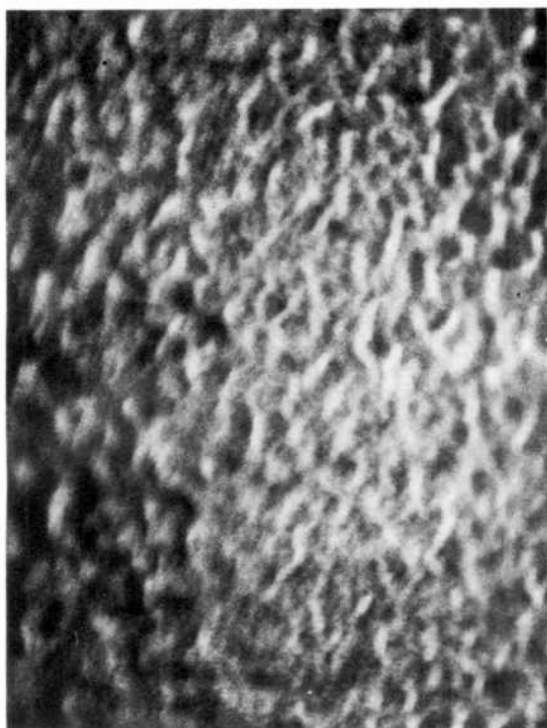


Fig. 1 The anterior lens shagreen.

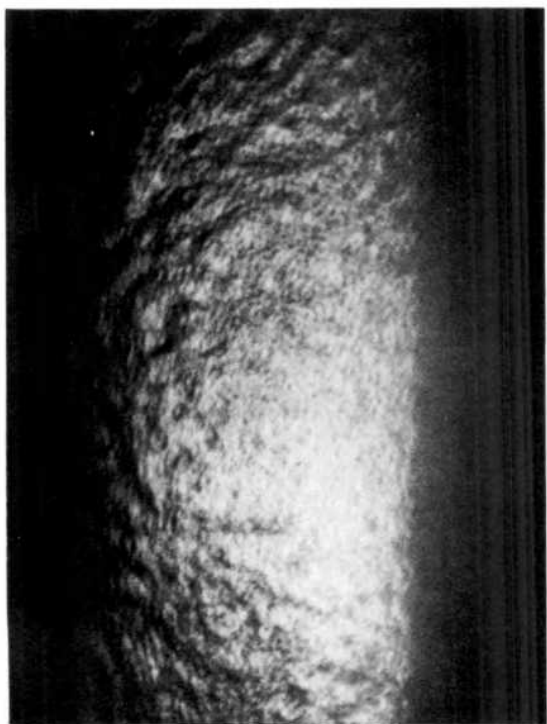


Fig. 2 The specular reflex image of the lens epithelium.

makes it particularly relevant to try to understand the structural form of the lens fibre.

The present study aims to estimate the width of the lens fibre in vivo and the extent of the taper and flare in the various regions of the fibre to give an overall picture of the shape of the typical human lens fibre on the anterior surface of the lens.

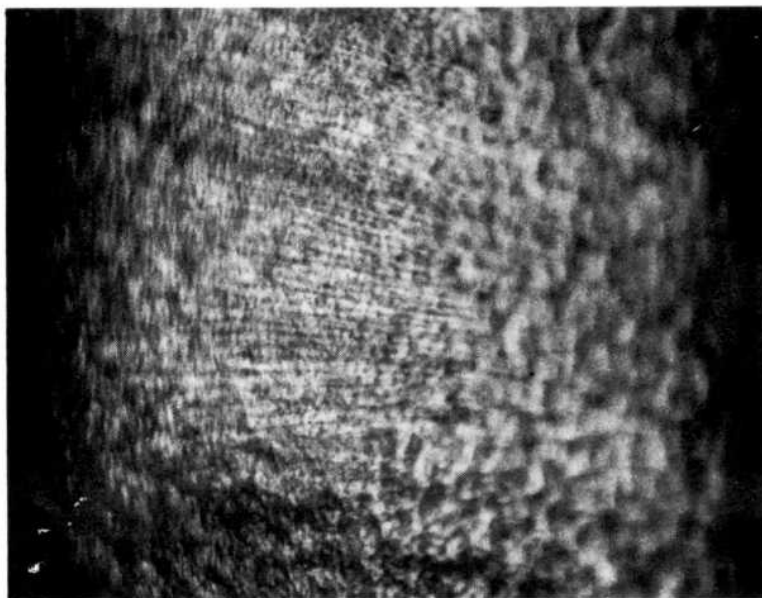
Material and methods

Sixty-five subjects were studied, ranging in age from 11 to 75, including 20 diabetics and two acromegalics. Twelve of the subjects had cataract. The observations were confined to one eye of each subject to reduce the effect of similarity between the left and right eyes detracting from the results. Recruitment of older subjects was limited by the difficulty in demonstrating the lens fibre specular reflex image, which could be found more reliably in young subjects. This image was also difficult to demonstrate in cataract, especially when there was any anterior subcapsular involvement. The eyes were photographed with a macro camera,* with the primary magnification increased to approximately 15:1. Experiments with an artificial eye† fitted with a graticule to represent the anterior lens surface showed that the magnification was increased by the effect of the cornea and with a camera viewing angle of 20° to the optic axis; the measured magnification was 14.8 horizontally and 17.0 vertically, giving a mean magnification of 15.9 times. The horizontal magnification of 14.8 was applied to the measurement of the fibre width of vertically running lens fibres. The vertical magnification of 17.0 was applied to the measurement of the fibre width of horizontally running lens fibres, and the mean magnification of 15.9 was applied to the measurement of obliquely running lens fibres. Most of the fibres satisfactorily demonstrated by the specular reflex image were horizontal or oblique.

The pupils were dilated with cyclopentolate 1% and phenylephrine 10% eye drops, and the subjects were seated at a Zeiss photo-slit lamp fitted with a Brown macro camera. The angles of illumination and viewing were adjusted to show the lens fibre specular reflex image. This was usually best demonstrated with broad slit focal illumination 20° off the optic axis on one side and the camera at 20° off the optic axis on the other side. The illumination and camera could be moved together to the left or right in order to demonstrate specular reflex images in the central or peripheral parts of the anterior lens surface. The peripheral images were identified by the presence of the pupil margin towards the edge of the frame. The pupil diameters varied from 6 to 8 mm.

The aperture on the 25 mm Leitz Photar macro lens was *f*5.6 and the film used was Ilford XP1, which

Fig. 3 *The specular reflex image of the lens fibres.*



combines fine grain with extended exposure latitude. An orange filter, Wratten 22, was used to increase image contrast, probably by reducing scatter from subjacent layers of the lens.

The negatives were projected on to paper with a Zeiss (Jena) Documator at a measured magnification of 17.0 times. The borders of the lens fibres were seen in the projected negative image as near parallel dark

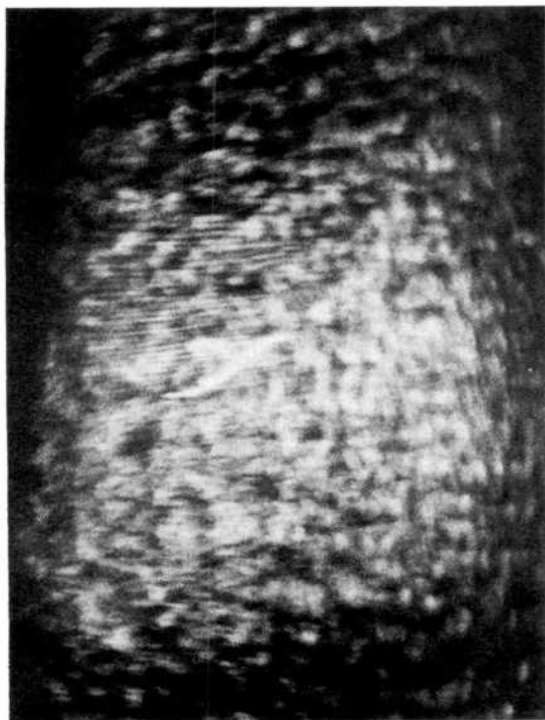


Fig. 4 *The specular reflex image of the lens fibres in the periphery of the lens.*

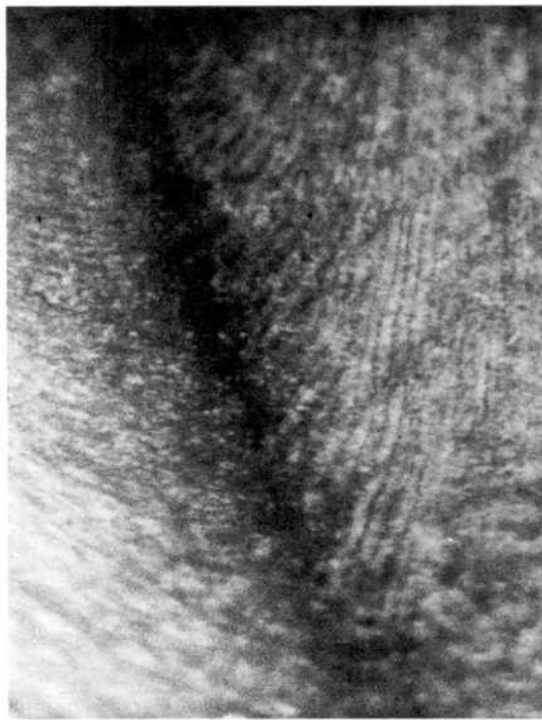


Fig. 5 *The lens fibres are seen to curve and to flare as they approach the lens suture, which is seen as a broad dark line.*

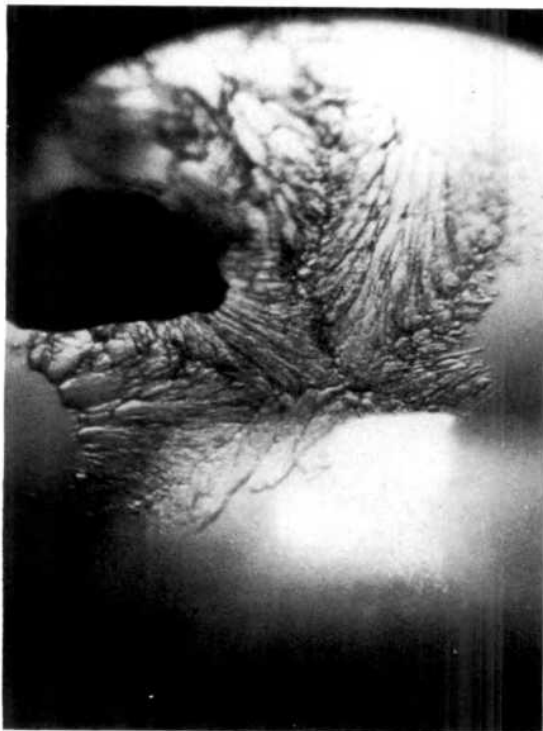


Fig. 6 The flare of the lens fibres as they approach the sutures is seen in exaggeration when they are affected by oedema in a recent traumatic cataract.

lines. These were drawn on to the paper with a fine pencil and the distance between the pencilled lines measured with a comparator, an instrument with a 10 times magnifying lens and a graticule scaled in 0.1

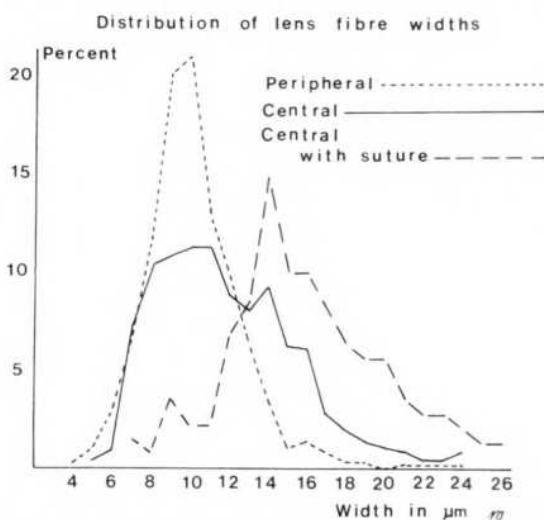


Fig. 7A Percentage distribution curves of fibre widths from the three regions of the lens.

mm divisions. In each fibre that could be traced for a distance of 100 μm or more, width measurements were made at 100 μm intervals. From these figures the state of fibre vergence could be calculated. This is stated as tapering (converging in the direction of the suture) or flaring (diverging in the direction of the suture); 1420 fibres were measured.

The measured fibres were arranged into three population groups: (1) peripheral fibres, identified by the image of the pupil margin towards the edge of the frame; (2) central fibres; (3) central fibres in region of a visible suture. The peripheral fibres were estimated to lie in the region of 3 to 3.75 mm radius of the anterior surface of the lens, the central fibres in the region of 1.5–2.5 mm radius, and the central fibres with suture in the region of 1–2 mm radius. In 29 eyes a second satisfactory negative of the same region of the lens was available, allowing calculations of the standard deviation for the method.

Results

The three population groups from the different regions of the anterior surface of the lens were found to show different characteristics. The mean width of the peripheral fibres was 10.2 μm , the central group 11.9 μm , and the central group with suture 15.8 μm . One-way analysis of variance showed that differences in the means for the three groups were highly significant ($p < 10^{-6}$).

The range of fibre sizes found in each of these populations also differed. Those in the peripheral group were the most homogeneous and those in the

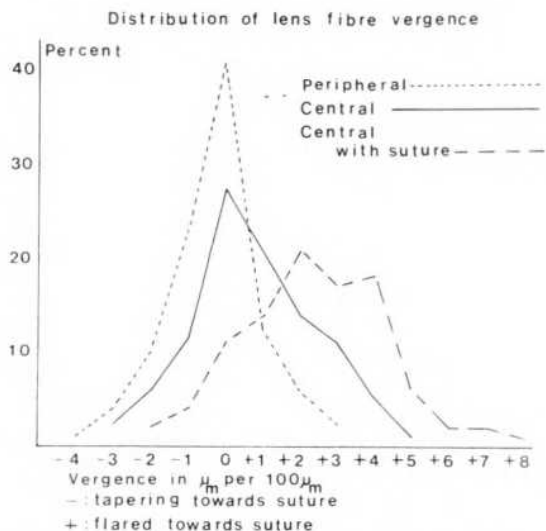


Fig. 7B Percentage distribution curves of fibre taper (–) and flare (+) from the three regions of the lens.

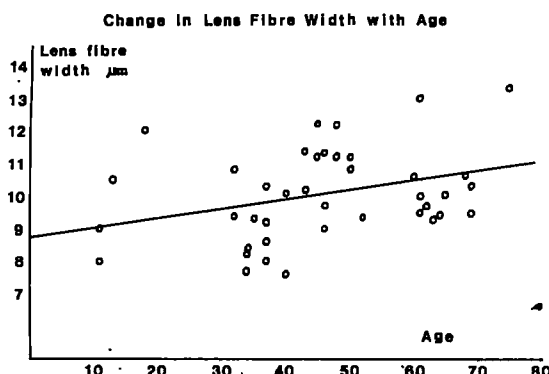


Fig. 8 The change in lens fibre size with age in peripheral fibres.

central group with suture showed the widest variation in size. These results are shown in the percentage distribution curves in Fig. 7A. The vergence also differed between the three fibre groups with the peripheral fibre group showing a mean taper of $-0.3 \mu\text{m}$ per $100 \mu\text{m}$, the central group a mean flare of $+0.6 \mu\text{m}$ per $100 \mu\text{m}$, and the central group with suture showed a mean flare of $+2.4 \mu\text{m}$ per $100 \mu\text{m}$. One-way analysis of variance showed that differences in the means of the three groups were highly significant ($p < 10^{-4}$).

In each negative examined both tapering and flaring fibres could commonly be found in any one region of the lens, but one or other type would predominate. Individual fibres tend either to taper or

to flare, but sometimes showed these characteristics separately in different regions of the same fibre. The percentage distribution curves for fibre taper and flare are shown in Fig. 7B.

The effect of age on the fibre size is shown graphically in Fig. 8. The mean peripheral fibre width in individual eyes was plotted against age. It is seen that there was a small ($0.028 \mu\text{m}$ per year) mean increase in lens fibre width with age. The regression analysis showed that this was significant ($p < 0.042$).

Eleven diabetic subjects were matched for age and sex with non-diabetics. The mean age for the diabetic subjects was 52.4 and for non-diabetics 52.7. The mean width of the peripheral lens fibres in the diabetics was $10.38 \mu\text{m}$ and in the non-diabetics $10.56 \mu\text{m}$, showing no significant difference ($p.63$).

The standard deviation for measuring the mean lens fibre width in a particular region of an individual lens was calculated from 29 eyes in which there were paired observations of the same region of the lens. This gave a standard deviation of $0.4 \mu\text{m}$. Thus it is seen that the change in lens fibre size with age (Fig. 3) exceeds the standard deviation for the method.

ESTIMATION OF THE SHAPE OF THE LENS FIBRE

From the observations of the lens fibre width in various regions of the lens and from the observations of the degree of taper or flare of the lens fibre in these regions it has been possible to construct a diagram of the typical lens fibre (Fig. 9). It is assumed that the adult lens has a diameter of approximately 10 mm, which is based on the calculations of Storey and Rabie,¹⁰ who estimated the diameter of the young adult lens unaccommodated at 9.6 mm. With good mydriasis the pupil diameter reaches 8 mm, so that the iris covers the peripheral 1 mm of the lens. The typical peripheral lens fibre has a width of $10 \mu\text{m}$ as it emerges from under the iris at a radius of 4 mm, tapering to $9 \mu\text{m}$ at 3.2 mm radius, and then running a near parallel sided course until becoming affected by progressively increasing flare as the suture is approached, with a final width of $20 \mu\text{m}$ reaching the suture. Thus the typical fibre flares by $9\text{--}20 \mu\text{m}$, a ratio of about 1:2. It is also seen (Fig. 9) that the fibre curves as it approaches the suture, except for those fibres that run to a suture bifurcation, which remain straight. The overall shape of groups of 25 typical lens fibres is shown in Fig. 9 (it is necessary to show a group of 25 fibres, since it is not feasible to draw single fibres).

From the estimated average fibre width of $10 \mu\text{m}$ at a diameter of 8 mm it is calculated that there are on average 2500 fibres in the most superficial shell of fibres.

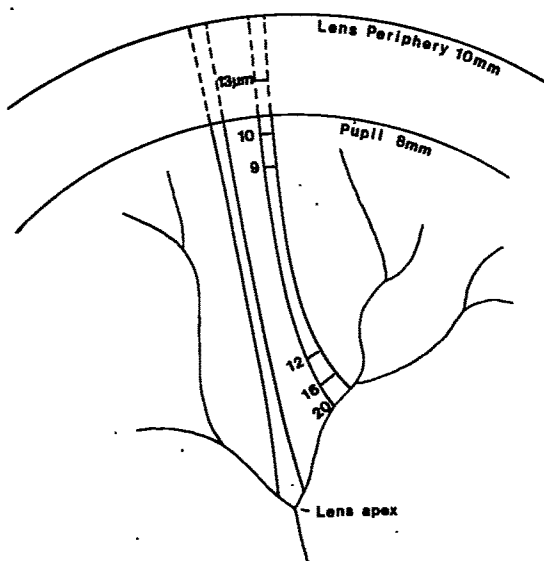
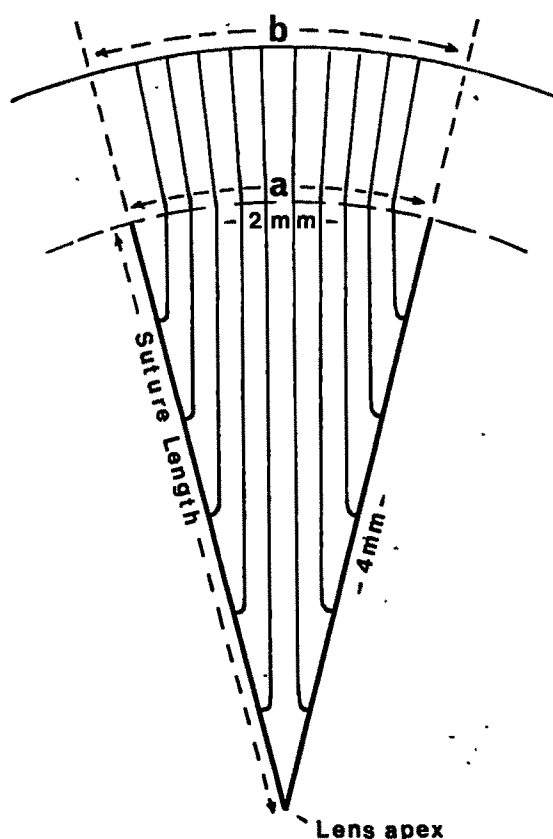


Fig. 9 The estimated shape of the typical lens fibre. Groups of 25 fibres are drawn.



a Intersutural arc length
b Equatorial arc length
 Fig. 10A A hypothetical lens fibre system in which the fibres curve sufficiently to join the sutures perpendicularly. This system requires that the fibres flare by 1:4.

ANALYSIS OF ERRORS

The method is subject to error owing to the observer having to identify the borders between adjacent fibres, which may occasionally lead to the false identification of non-adjacent fibre borders and the measurement of two fibres as one. Thus this may occasionally cause overestimation of the lens fibre width.

The fibres are observed through the cornea, and the distortions imposed by that structure have been allowed for by the use of an artificial eye, but the effect of various anterior chamber depths was not examined.

Discussion

The present in-vivo study confirms the observations by Vogt¹ on the fibre shape which he observed in a

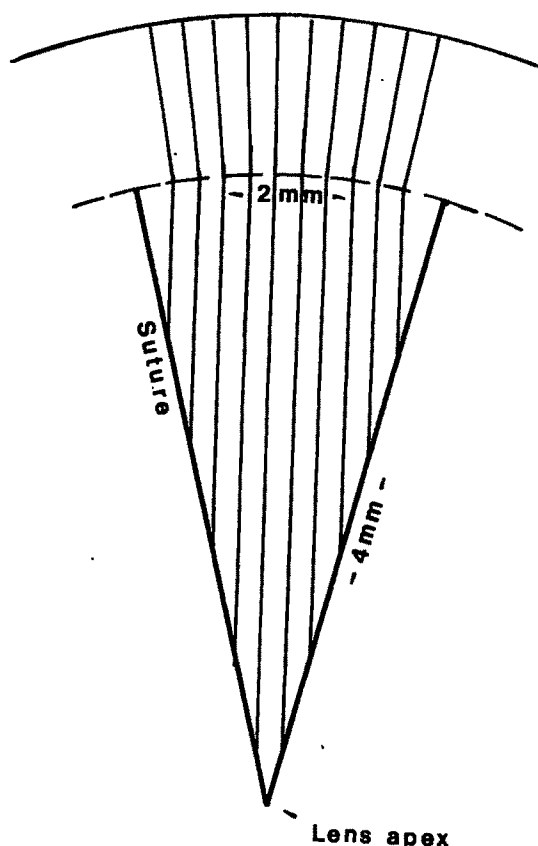


Fig. 10B A hypothetical lens fibre system in which the fibres run a straight course to join the sutures at an angle of 14°. The fibres in this system do not need to flare.

single lens of a child's eye in vitro. It is shown that the fibre tapers slightly in the periphery of the lens and then runs a gradually increasingly flaring course towards the suture. In addition it has been possible to estimate the width in various regions of the fibre. Recent studies³ appear to have concentrated on the central flaring region of the lens and have not demonstrated the existence of a taper from periphery to centre.

The key to the mechanism of fibre taper and flare is the dimensions of the lens suture system. The sutures in the adult human eye show an extensively branched system¹¹ (Fig. 9). The peripheral terminations of the sutures are some distance from the equatorial periphery of the lens; thus the arc length between the termination of one suture and the next one is less than the arc length of the same segment of the lens at the equator (Fig. 10A). Then the fibres must taper as

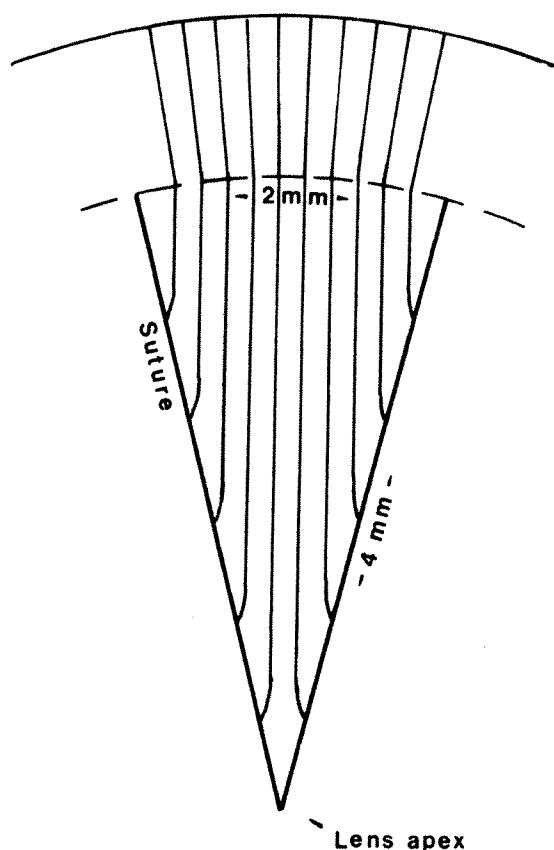


Fig. 10C A diagrammatic representation of the actual human lens fibre system in which the fibres curve to join the sutures at an angle of 30° and flare by 1:2.

they pass from the equator to enter the bottleneck between the suture terminations. The shape of the fibres in the next part of their course is determined by the difference in the arc length between the suture terminations and the lengths of the sutures themselves. This varies somewhat in different regions of the lens depending on the degree of suture branching in that region. The differences are at their most extreme for fibres that run towards the apex of the lens (Fig. 9) and least for fibres that terminate near the peripheral extent of the sutures. The ratio of the arc length between the suture termination to the length of the sutures themselves in Fig. 9 is 1:4. This could be taken to imply that each fibre should flare by a factor of 4, which is approximately twice the value that measurement of the fibres has shown. The fibres would have to flare by a factor of 4 if they were each to curve sufficiently to join the suture perpen-

dicularly, as is shown diagrammatically in Fig. 10A. But this is not the case, as is seen in the specular photograph (Fig. 5), which shows the fibres joining the suture obliquely. No fibre flare at all would be required if the fibres were to run a straight course and to join the suture at an acute angle of 14° (Fig. 10B). The measured flare at 2:1 is achieved when the fibres curve sufficiently to meet the suture at an angle of 30° (Fig. 10C), which demonstrates the typical arrangement in the human lens.

The lens fibre and its relationship to the suture presents a most intriguing shape, with evident variation between individual fibres and between the fibres in various regions of the lens. It appears that versatility of the lens fibre allows a beautifully geometrically symmetrical lens to be assembled from a very asymmetric fibre and suture system.

An increase in the lens fibre width with age would occur if the total number of lens fibres in the anterior superficial shell (estimated at 25000) remains constant, and this appears to be the case.

No differences in lens fibre width between normal persons and diabetics have been demonstrated, though the number of diabetic lenses that could be satisfactorily measured were small. This suggests that it is not a wider lens fibre that accounts for the greater lens fibre size for age that has been observed in the diabetic.¹²

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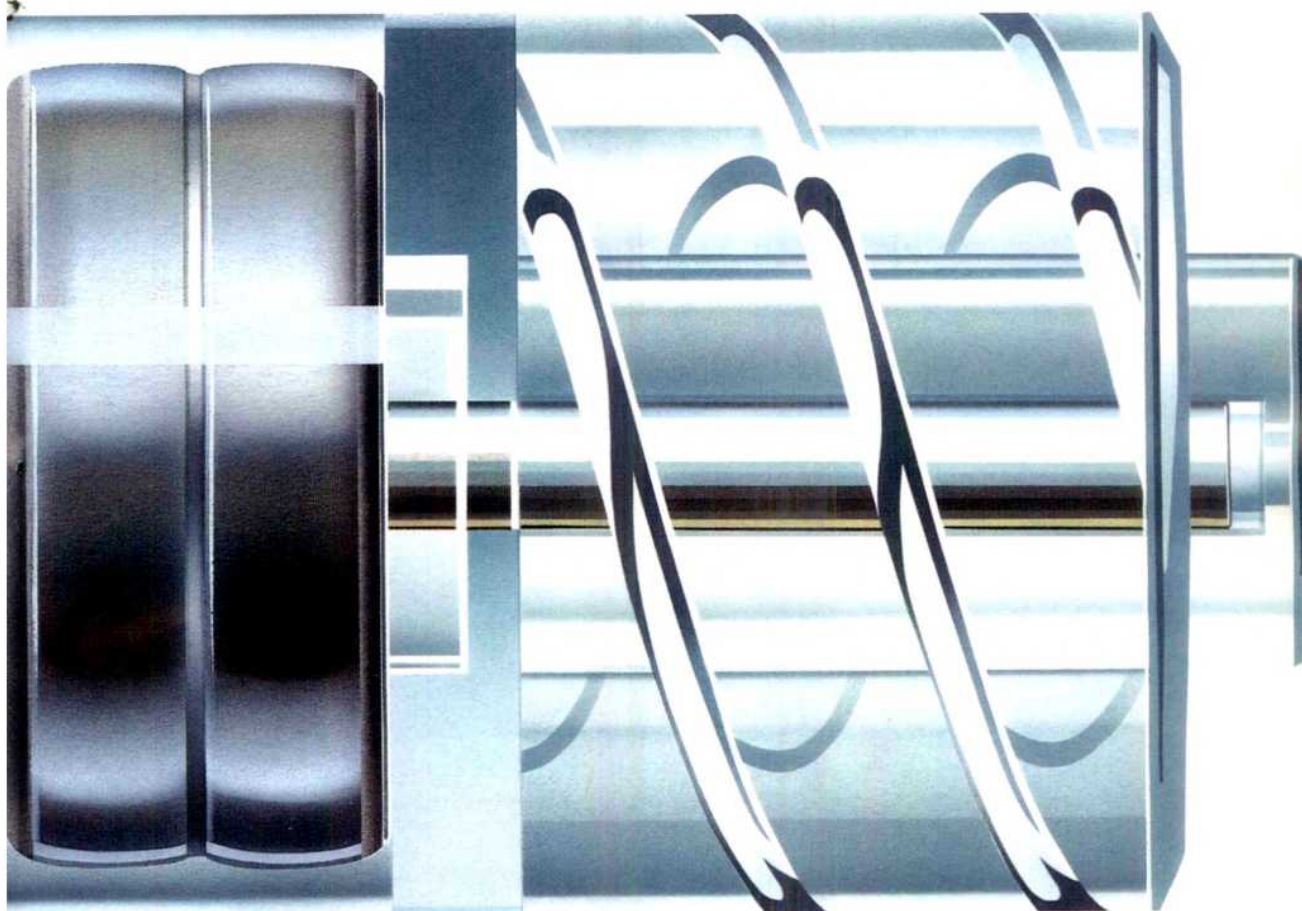
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A new Snellen's visual acuity chart with 'Indian' numerals

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SUMMARY 'Indian' numerals, which are popular among the Arab population, were used to devise a new Snellen's visual acuity chart. The new chart has the advantages of a reading chart. It keeps the patient's interest, does not miss alexic patients, and is quicker to perform. It is also devoid of the many disadvantages of a kinetic response chart (the capital E letter or Landolt's broken rings), especially that of the limited option of test objects.

Snellen's concept for testing visual acuity is widely used today. Each of the constituent parts of the letters used subtends a visual angle of one minute of arc at the eye, at the standard viewing distance. The minimum resolvable visual angle is taken as the visual acuity which is designated according to Snellen's classical formula $V=d/D$, where d is the distance at which the letters are read and D that at which they should be read.^{1,2}

What matters in a visual acuity test object is its ability as a geometrical pattern to test refractive or retinal functions.³ However, the recognition of letters is a perceptive process with strong personal factors. For this reason many alternatives have been proposed, especially in countries which do not have Roman script, and these are quite necessary when the subject is illiterate. Arabic numerals and the capital E letter provide possible substitutes. But the most popular suggestion which does not depend upon letters is that of Landolt's broken rings.¹

In Middle East countries the capital E letter and Landolt's rings test charts are widely used. But they have several disadvantages. First, these charts contain test objects with only four possible options, and they are likely to be guessed or memorised. For official examinations such charts are not recommended.³ Secondly, they require some considerable time to explain to the patient how to perform the test. Thirdly, in Landolt's rings it is probable that the gap is recognised by increased illumination in its position before its form is clearly discerned, so that a higher value is obtained than in fact exists.¹ Fourthly, Landolt's rings also overestimate the visual acuity of

patients with uncorrected astigmatism because of the absence of vertical and horizontal lines.⁴ Fifthly, the unfamiliarity of the test objects lacks the interest of reading letters or numerals.

We therefore describe a Snellen's chart utilising 'Indian' numerals. It has the advantage of a reading chart but is devoid of the disadvantages of the capital E letter or Landolt's broken rings.

Material and methods

For the calculation of the size of any test object on Snellen's chart at a specified distance in such a way that its details subtend one minute of arc at that distance the tangent of one minute, which is equal to 0.000291, is multiplied by that distance in millimeters. The result is the single unit of the object in millimeters. When this value is multiplied by 5 the result is the whole length of the square of that object. For example, at a distance of 24 meters, the single unit of the object is equal to $0.000291 \times 24\,000$ ($=6.984$ mm) and the whole object is equal to 6.984×5 ($=34.92$ mm). In reality it is approximated to 7.0 mm and 35 mm respectively and so on.

DESCRIPTION OF THE CHART (Fig. 1)

- (1) Two digit numerals were chosen.
- (2) Each was drawn in a five-unit square to subtend five minutes of arc at the eye, at the specified distance.
- (3) The thickness of the lines is equal to the gaps in between and each is one-fifth of the whole square.
- (4) The test numerals were arranged on the same gradation in size of letters as that of Snellen's chart, that is, at 60 m, 36 m . . . down to 4 m.

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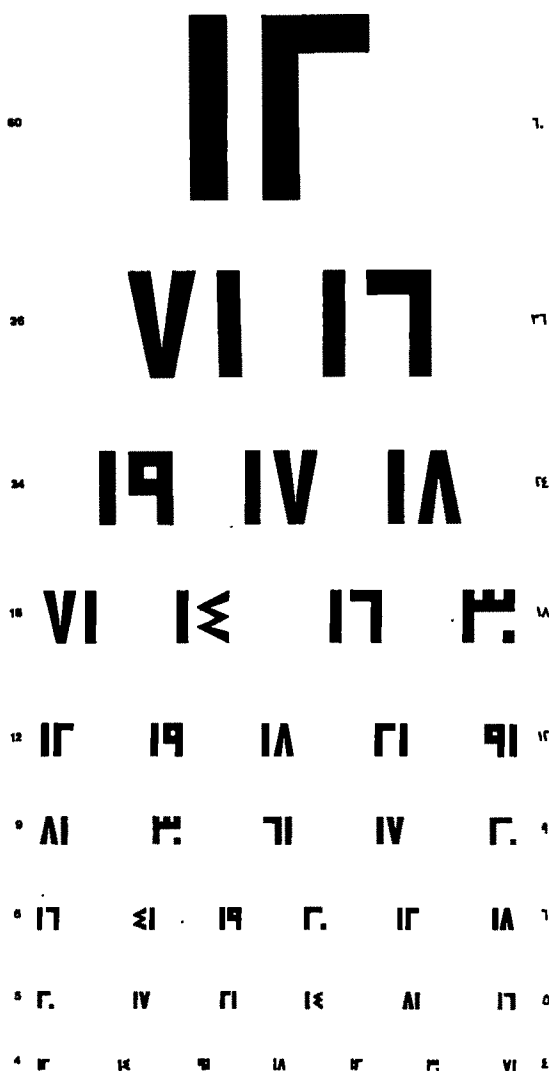


Fig. Photograph of a Snellen chart with Indian numerals reduced to one-seventh.

(5) A high-contrast black colour is used for printing the numerals on white sheets of durable material. These can also be delivered on white opal plastic (Perspex), for even illumination from behind and to fit in Snellen's chart stand.

(6) The specified distance at which a numeral is to be read is written in small figures, in Arabic numbers to the left hand side and Indian numbers to the right hand side of the chart.

Several charts were made with different arrangements of numerals; also charts for reverse use with mirrors in case of space limitation were made.

One hundred and forty patients were examined by

both the new Indian numerals chart and the capital E letter test chart for comparison.

Results

We compared the visual acuity tested with the new Indian numerals and with the capital E letter Snellen's acuity chart in 140 patients. Their ages varied from 6 to 62 years and their visual acuities from 3/60 to 6/5. Four patients (2.8%) failed to read the new chart. The results from 270 eyes in the remaining 136 patients are shown in Table 1.

Discussion

Testing visual acuity with a reading chart excites a verbal response, while testing with Landolt's rings or the capital E letter excites a kinetic response (pointing by the hand towards the direction of the gap). The verbal response to seeing an object involves a complex neurological pathway,⁵ but the kinetic response is a much simpler one. Thus young children usually score a better visual acuity with tests such as the E letter, which tests the resolving power, than with letters or numerals, which demand interpretation as well.⁶ Moreover, alexic (word blind) patients are likely to be missed when examined by the E letter or Landolt's rings charts alone. For these reasons, and for convenience and to save time, visual acuity charts with either letters or numerals to read are preferred.

Emarah has suggested a reading Snellen's chart with vertical and horizontal predominant lines based on Arabic alphabets to disclose all possible amounts of astigmatism,⁷ but the configuration of letters made the test difficult even for average literate individuals. In addition the presence of many of ophthalmologists and opticians practising in the Middle East whose mother tongue is not Arabic made the test unpopular.

Arabic numerals have not been used as a substitute for letters in Arab countries because they were abandoned long ago, and the so-called Indian numerals are in use nowadays instead of them.⁸ These can be recognised by most of the population, even illiterate people.

Table 1 Comparison of visual acuity with the E letter and with Indian numerals test charts in 270 eyes

			No.	%
Equal visual acuity			183	67.8
Deviation from the E letter test	Worse	Better		
One line difference	42	17	59	21.8
More than one line difference	18	10	28	10.4
Total	60	27	270	100

Visual acuity tested with the Indian numerals chart correlates well with the E letter chart. 89.6% of tested eyes had equal vision or one line difference. But the numerals were slightly more difficult than the E letter test. A greater number of eyes scored worse visual acuities with them. However, we think that a reading Snellen's chart with Indian numerals would be useful for testing visual acuity in Arab patients because it is devoid of the disadvantages of a kinetic response chart, easier to recognise than Arabic alphabets, and still has the advantages of a reading chart.

I am grateful to medical artist Miss Raba Abdul-Fattah Ali from the Medical illustration Department of the Ministry of Public Health, Kuwait, for the technical assistance in preparing the chart, and to Dr David Wright for reviewing the manuscript.

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Isolated foveal hypoplasia

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SUMMARY Fifteen patients presented with foveal hypoplasia as an isolated ocular finding. The characteristic findings associated with this entity are a visual acuity of 6/21 or worse, nystagmus, and a typical ophthalmoscopic appearance of the macular area, including absent or abnormal maculofoveal reflexes, unclear definition of the maculofoveal area, and capillaries running abnormally close to the presumed macular area, some of them even crossing the horizontal meridian. Fluorescein angiography revealed a variable and incomplete filtering effect of the choroidal fluorescence in the macular area, suggesting abnormalities in the amount and distribution of macular pigments. The fundal findings of isolated foveal hypoplasia, although typical, are very subtle and often difficult to detect, especially because of the accompanying nystagmus. For this reason we suspect that foveal hypoplasia may be more common than is generally believed.

Foveal hypoplasia has been described in association with other anatomical eye disorders, such as aniridia, albinism, microphthalmus, and achromatopsia.¹⁻³ Recently Yoshizumi *et al.*⁴ described a patient with congenital pendular nystagmus, foveal hypoplasia, and bilateral retinal rosettes near the ora serrata. O'Donnell and Pappas⁵ described a family with congenital nystagmus and mild foveal hypoplasia associated with presenile cataracts and peripheral corneal pannus.

Only a few cases of foveal hypoplasia as an isolated anatomical finding have been reported.⁶⁻⁹ Holm⁶ described three brothers with nystagmus and foveal hypoplasia; Koyanagi⁷ reported similar findings in a brother and a sister. Uemura and Kumanomido⁸ described seven patients with foveal hypoplasia and nystagmus. Recently Curran and Robb⁹ described nine patients with foveal hypoplasia and congenital nystagmus.

We report here on the clinical and laboratory findings in 15 patients with bilateral foveal hypoplasia as an isolated anatomical finding.

Subjects and methods

Fifteen patients with foveal hypoplasia, congenital

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nystagmus, and low visual acuity, but without evidence of other ocular disorders, were examined and followed up in the Eye Outpatient Department of the Kaplan Hospital, Rehovot.

In each patient cycloplegic refraction was determined after the instillation of 2% cyclopentolate drops twice at an interval of half an hour. Subjective refraction was determined a week later. Orthoptic examination, evaluation of colour vision by means of pseudoisochromatic plates, and several dilated fundus examinations were performed in each case. Fluorescein angiography was performed in only seven patients, who were old enough to co-operate. Electroretinograms (ERG) and the visual evoked response (VER) were recorded and measured with the Nicolet CA 1000 apparatus.

Genetic studies of the families of the affected patients were carried out wherever possible. The pedigrees of nine families were investigated and a total of 35 individuals, including the 15 patients of this series, were examined. The family pedigrees of three of our patients could not be obtained.

Results

Of the 15 patients included in this study six were males and nine were females (Table 1). Their ages ranged from 3 to 46 years. All patients were bilater-

Table 1 Clinical data of patients with isolated foveal hypoplasia

Patient no., sex, age (yr)	Visual acuity	Refraction	Colour vision	Orthoptic examination	Electrodiagnostic tests
1, F, 12	6/21	+2.50=+3.00×85	Normal	Orthophoria	Large ERG components, normal latency but subnormal amplitude of VER
2, M, 9	6/21	+4.50=+4.25×95	Protanopia	Orthophoria	Large ERG components, normal latency but subnormal amplitude of VER
3, F, 11	6/60	+3.50=+3.00×90	Normal	Alternating Esotropia +18°	Normal ERG, normal latency but subnormal amplitude of VER
4, F, 9	6/60	+4.00=+3.00×90	Normal	Intermittent Exotropia -30°	Normal latency but subnormal amplitude of VER
5, F, 5	6/60	-2.00=+5.50×90	Normal	Exotropia -30°	Normal ERG
6, M, 3	6/60	-1.50=+3.50×100	Not evaluated	Orthophoria	Normal ERG
7, F, 10	6/60	-2.00=+2.50×120	Normal	Orthophoria	Normal ERG, normal latency but subnormal amplitude of VER
8, M, 6	6/60	-0.50=+1.50×90	Normal	Esotropia +30°	Normal ERG, normal latency but subnormal amplitude of VER
9, M, 10	6/21	-0.25=+2.75×100	Normal	Exotropia -30°	Normal ERG, normal latency but subnormal amplitude of VER
10, F, 18	6/60	+0.25=+2.50×90	Normal	Esotropia +30°	Normal ERG, normal latency but subnormal amplitude of VER
11, F, 7	6/60	Plano=+3.00×100	Normal	Orthophoria	Not recorded
12, M, 18	6/60	Plano=+3.00×100	Normal	Exotropia -20°	Normal ERG, normal latency but subnormal amplitude of VER
13, F, 32	6/60	Plano=+3.00×100	Normal	Exotropia -20°	Normal ERG, normal latency but subnormal amplitude of VER
14, F, 46	6/60	Plano=+2.00×180	Normal	Orthophoria	Not recorded
15, M, 27	6/60	Plano=+2.00×180	Normal	Exotropia >-45°	Normal ERG, normal latency but subnormal amplitude of VER

ally affected by the disease, and all presented with either pendular or jerk nystagmus which remained horizontal even in vertical gaze. The best corrected visual acuity was in no case better than 6/21; it was 6/60 in six patients, 6/30 in five others, and 6/21 in four. Cycloplegic refraction revealed that 13 eyes (seven patients) had with-the-rule astigmatism of 3.00 dioptres or more. Colour vision was normal in 13 patients, and one male patient had protanopia; one child was too young to be tested. Twelve patients had abnormal head posture, but no typical pattern was evident. Tropia was found in nine patients, esotropia in three of them and exotropia in six.

Indirect ophthalmoscopic examination showed characteristic fundal findings as follows: nerve heads were bilaterally normal; macular and foveal reflexes were absent or abnormal; the retinal capillaries which run from the upper and lower arcades were abnormally close to the presumed foveal area, and some of them even crossed the horizontal meridian (Figs. 1, 2). In two of the seven fluorescein angiograms the intensity of choroidal fluorescence emitted from the presumed macular area was similar to that from other fundal areas (Fig. 3). In four cases, although pigment was evidently present in the

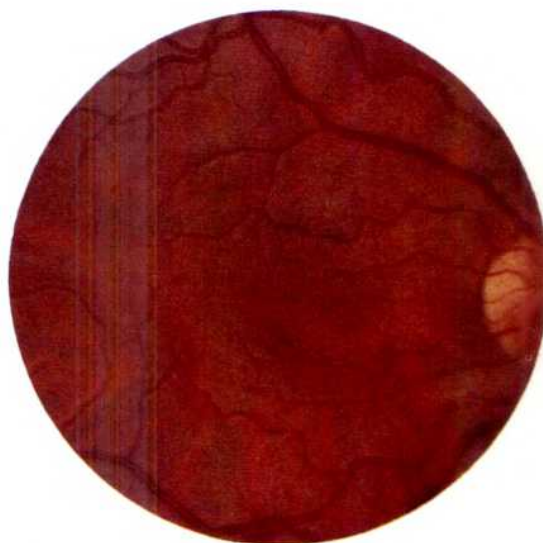


Fig. 1 Fundal appearance of a 9-year-old boy with isolated foveal hypoplasia. Macular and foveal reflexes are absent. The retinal capillaries which run from the upper and lower arcades are abnormally close to the presumed foveal area, and some of them cross the horizontal meridian.

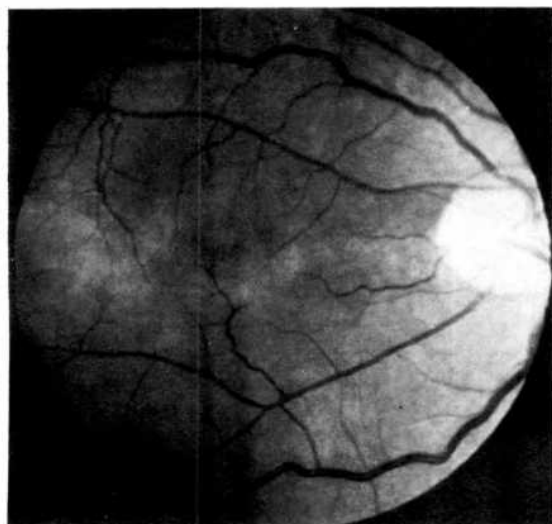


Fig. 2 Red-free picture of the macular area. The maculofoveal area is poorly defined. Capillaries from the upper and lower arcades are abnormally close to the presumed macular area and some of them cross the horizontal meridian.

macular area, there was not enough of it completely to filter the fluorescence from the underlying choroid. In one patient the filtering of the choroidal fluorescence in the macular area was total.

The ERG was performed on 12 patients under photopic conditions and followed for about 15

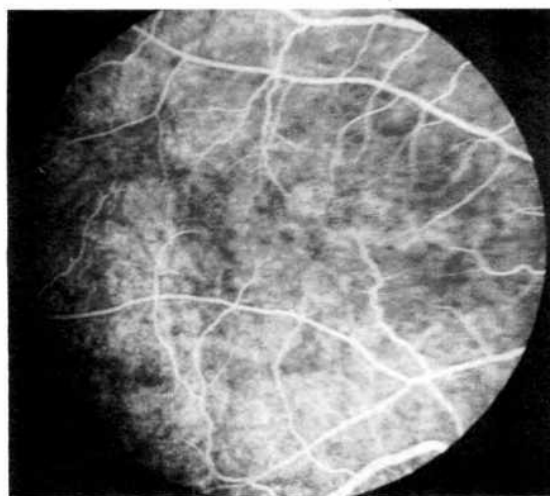


Fig. 3 Fluorescein angiography of the fundus in Fig. 2. The choroidal fluorescence from the maculofoveal area is similar to that from more peripheral parts of the fundus. The normal filter effect associated with the presence of pigments in the macular area is absent.

minutes in the dark; full dark adaptation was difficult to achieve. Both photopic and scotopic ERG components were found to be normal in 10 patients and unusually large in two. The VER was determined in 11 patients, all of whom showed normal latency though with slightly subnormal amplitudes.

In the nine families whose pedigrees were studied there were three pairs of affected siblings. We examined 20 additional members of these families, none of whom had foveal hypoplasia. Eight individuals from these families were reported to have some form of visual disturbances, but were not examined, and the possibility that some or all of them had foveal hypoplasia cannot be ruled out. Family members studied were of different ethnic origins, and there were four cases of consanguinity (Fig. 4).

Discussion

In the absence of other ocular diseases the diagnostic findings common to all patients with foveal hypoplasia are a low visual acuity, never better than 6/21; jerk or pendular nystagmus; and typical ophthalmoscopic and angiographic findings, as discussed below.

Waardenburg¹ described the characteristic fundal appearance in foveal hypoplasia as absence or marked irregularity of foveal and perifoveal reflexes; irregular distribution of the capillary ends; complete or almost complete absence of macular yellow. The first two features in this description are consistent with our own observations on the appearance of the maculofoveal area. The macular and foveal reflexes were absent or abnormal in all our patients, and the retinal capillaries were abnormally close to the presumed foveal area. In some cases these capillaries even crossed the horizontal meridian, with resulting absence of the avascular zone typical of the normal macula (Figs. 1, 2). In two patients the fluorescein angiography pattern from the presumed macular area was similar to that emitted from more peripheral parts of the fundus, probably because of the absence of macular pigments which would normally filter the background choroidal fluorescence (Fig. 3). In the other five varying amounts of fluorescence were emitted from the presumed macular areas. On the basis of our findings we assume that the fluorescein angiographic appearance of the maculofoveal area probably varies in different patients and depends on the amount of macular pigment present. This conclusion does not entirely corroborate Waardenburg's contention that macular pigment is totally or almost totally absent.

Our patients showed a high incidence of tropias (9/15) and abnormal head postures (12/15). Since the overall prevalence of tropias in the general population is not higher than 3%,¹⁰ and the incidence of

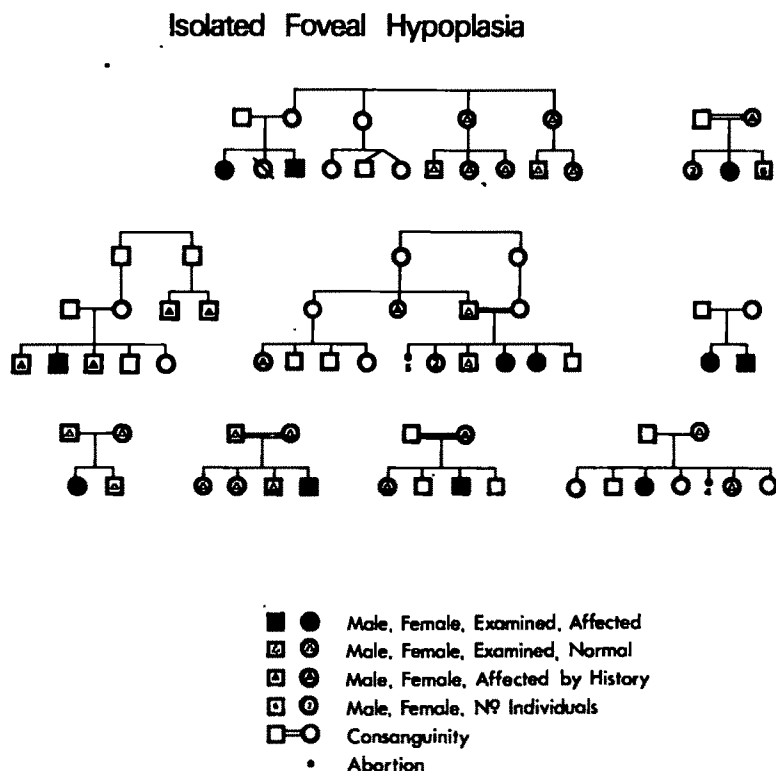


Fig. 4 Pedigrees of nine families. Three patients were unable to supply genetic data.

abnormal head posture is probably even lower, it is highly probable that the frequent occurrence of these findings in our patients is associated with foveal hypoplasia.

Ten of the 12 patients who underwent ERG achieved normal results. This, together with their normal colour vision, indicates that their retinal function was normal but does not exclude the possible existence of a localised foveal defect which remains undetected in the overall ERG response. The normal latency and slightly diminished amplitude revealed by the VER is suggestive of impaired foveal function but normal nervous conduction in this disorder.

Impaired visual acuity and macular anomalies are often found to be correlated with abnormal colour vision. The finding of normal colour vision in all but one of the patients treated is therefore surprising, though a similar lack of correlation between visual acuity and colour vision is also found in some other diseases, such as ocular albinism.¹¹ More sophisticated tests might have revealed defects in colour vision undetectable by the pseudoisochromatic plates. However, since most of our patients were small children with low visual acuity, such tests could not be employed.

Foveal hypoplasia has been reported in association with albinism, aniridia, and occasionally achromatopsia.¹⁻³ None of our 15 patients was albinotic in appearance. In all cases the irides were of normal appearance and did not transilluminate. The fact that nine of the patients were female also argues against a diagnosis of X-linked ocular albinism, since this disorder has rarely been reported in females. The defective colour vision and the pronounced photophobia characteristic of achromatopsia were absent. Other than foveal hypoplasia, with its accompanying nystagmus and low visual acuity, no anatomical ocular defects or systemic abnormalities were found. Nystagmus and low visual acuity in infancy may result from a number of factors, but when they are the sole findings which accompany the characteristic appearance of the fovea they should be helpful clinically in distinguishing isolated foveal hypoplasia from the other disorders mentioned above.

The literature contains only a few reports of foveal hypoplasia as an isolated anatomical finding.⁶⁻⁹ One such study was carried out by Curran and Robb;⁹ their findings were not significantly different from our own.

In a few cases of macular hypoplasia described by Duke-Elder² histological examination showed that

the retina at the posterior pole had remained at the stage of differentiation normally exhibited in the sixth month in utero. Hendrickson and Yuodelis¹² showed that a small foveal depression first develops in the fetus at 24–26 weeks, as the ganglion and inner nuclear layer cells move laterally. At birth the centre of the fovea contains only a single layer of short, thick cones with immature short outer segments. These authors concluded that the fovea normally achieves maturation between 15 and 45 months of age. It is possible that in our patients the structure of the retina in the central area resembles that at the periphery, showing persistence of ganglion cells and nuclear layers.

Henkind¹³ studied the development of the foveal avascular zone in experimental animals. He suggested that it occurs as a result of capillary closure after birth, is independent of vision, and that the vessels occasionally seen traversing this zone represent a persistence of the fetal vasculature. The above description might apply also to foveal hypoplasia, but confirmatory embryological and histological evidence is lacking.

No definite hereditary pattern could be established in our study. Autosomal recessive inheritance has been postulated.⁹ Although our findings do not contradict his possibility, they cannot be taken as confirmation. Isolated foveal hypoplasia is characterised by variable expressivity, and the gene appears to have a low degree of penetrance. Multifactorial inheritance should be considered as another possibility, because of the absence of a clear pattern of inheritance or obvious familial aggregation. The data obtained from the families of our patients seem rather to suggest that isolated foveal hypoplasia might be another example of genetic heterogeneity with different genetic and possibly also non-genetic aetiologies.

Although our patients showed poor visual acuity, functional capacity was quite satisfactory in each

case. The presence of nystagmus and poor vision in children and infants without any other ocular findings should prompt the ophthalmologist to carry out a thorough fundal examination of the maculofoveal area. The fundal findings in isolated foveal hypoplasia, though quite typical, are very subtle and often difficult to detect, especially because of the accompanying nystagmus. For this reason we suspect that foveal hypoplasia is more common than is generally believed.

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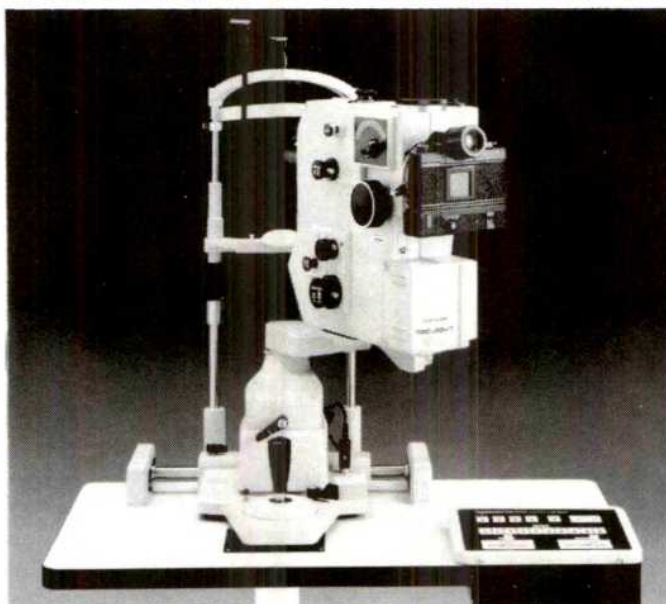
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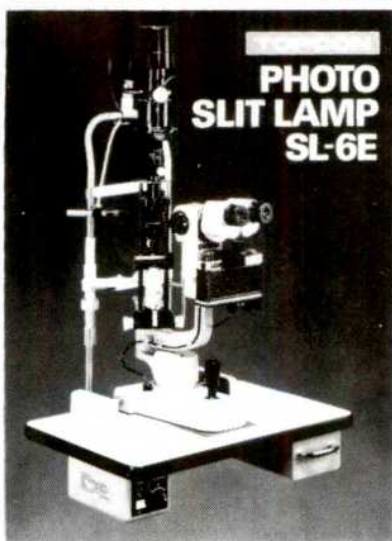
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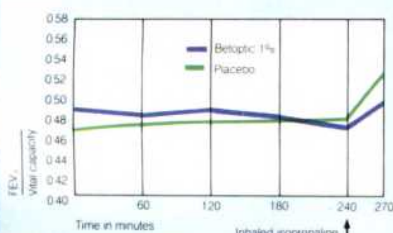
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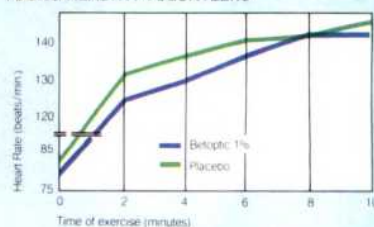
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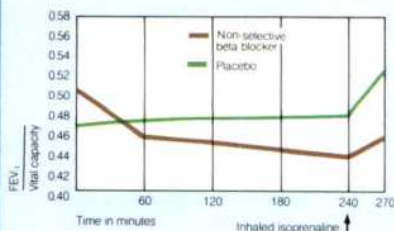


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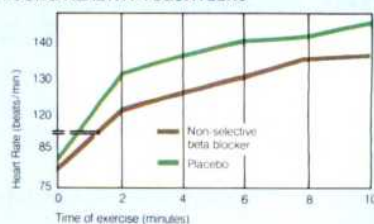
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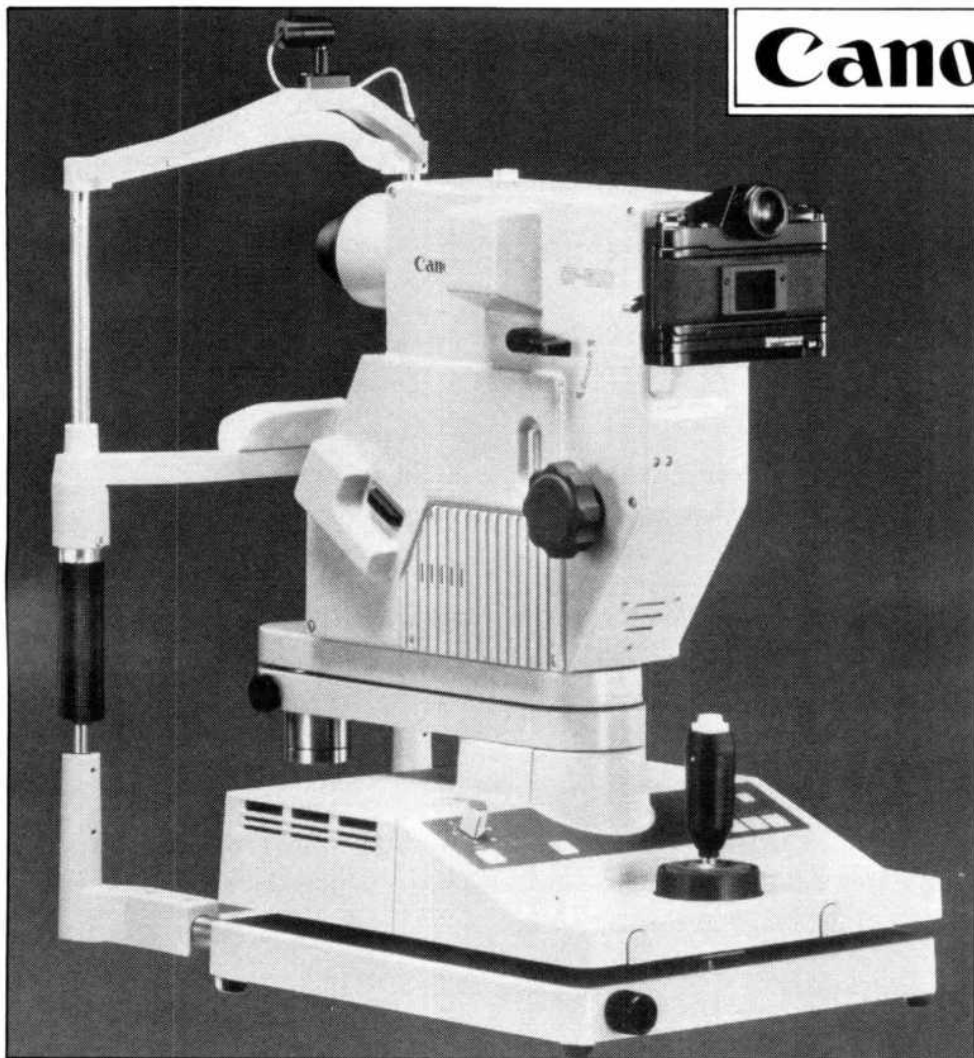
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Baton twirling: another cause of eye injury

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SUMMARY Baton twirling is an increasingly popular sport, with an estimated 5000 participants in Scotland alone. The baton, weighing over 200 g, is spun at high speeds and frequently thrown over 40 feet (12 m) into the air. We report a case of a 17-year-old girl who sustained a serious eye injury after being struck by a baton. The occurrence of eye injury has not been reported in this sport, and we discuss the potential for injury.

It is well recognised that sport accounts for a considerable percentage of eye injuries, particularly racket and contact sports.^{1,2} Baton twirling is a minority sport but its popularity is growing rapidly, and the potential for eye injury is high. Eye injury has not previously been reported, but this case illustrates the potential danger of the sport.

Case report

A 17-year-old girl was admitted having been struck in the left eye by one end of her falling baton. At the time of admission she had a tense orbital haematoma with periorbital bruising, proptosis, and marked chemosis. Traumatic mydriasis was present though no intraocular haemorrhage. X-rays showed a blow-out fracture of her left orbital floor. Her initial visual acuity was 6/60 due to a combination of optic nerve compression by the orbital haematoma and macular oedema. Her visual acuity was tested half hourly, and by the following morning vision had improved to 6/24, so that there was no need for orbital decompression. Subsequently vision improved to 6/18 after seven days and eventually to 6/6 at eight weeks.

Her eye movements were limited in all directions of gaze at the outset, a product of the orbital haematoma. As the haematoma resolved, eye movements improved, leaving only the limitation of elevation produced by the fracture. This settled satisfactorily spontaneously, and eight weeks after the accident eye movements were full and diplopia could not be elicited.

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Discussion

The sport of baton twirling is comparable to gymnastics and has shared that sports' recent growth in popularity. The participants tend to be girls of teenage and primary school age. The sport is governed by its National Federation, which organises tournaments with graded competition, and at the highest level international events are held. At present in Scotland there are 2000 registered competitors with an estimated further 8000 non-registered participants. To put it in context this overall figure of 10 000 can be compared to more popular sports: 80 000 people play squash in Scotland; 120 000 play tennis.³ Whereas the figures for squash and tennis are static, those for baton twirling have more than doubled in the last five years.

The sport involves spinning a baton about the head and body as well as throwing it into the air and catching it. On occasions the baton can be thrown as high as 15 m. The standard baton is 64 cm long, made of tubular steel with two hard rubber end-stops weighing 20 g and 30 g respectively, and an overall weight of 214 g. The diameters of the end-stops are 3 cm and 4 cm respectively, and both are capable of entering the orbit.

Table 1 Rotational force of baton

Spinning at 5 rev/s
Kinetic energy = $\frac{1}{2} I \omega^2$
$= \frac{1}{2} I (2\pi f)^2$
$= 5.3 \text{ J}$
Assuming displacement of eye of 1 cm:
Force of impact = 530 N

Table 2 Gravitational force of baton

Falling from 15 m	
Kinetic energy = mgh	
$= 0.214 \text{ kg} \times 9.8 \text{ ms}^{-1} \times 15 \text{ m}$	
$= 31.5 \text{ J}$	
Assuming displacement of eye of 1 cm:	
Force of impact $= 3150 \text{ N}$	
Force of rotation $= 3150 + 530$	
and gravity	$= 3680 \text{ N}$

Table 3 Force of a squash ball

Assuming ball travelling at 120 mph	
weighing 25 g:	
120 mph $= 54 \text{ ms}^{-1}$	
KE $= \frac{1}{2} M V^2$	
$= \frac{1}{2} \times 0.025 \text{ kg} \times (54 \text{ ms}^{-1})^2$	
$= 36.45 \text{ J}$	
Assuming displacement of eye of 1 cm:	
Force of impact $= 3645 \text{ N}$	

The baton cannot be spun faster than 5 revolutions/second and at this rate the force generated by the end of the baton is 530 N (Table 1). Similarly a baton falling from 15 m has a force of impact of 3150 N (Table 2). Thus the maximum force of a baton spinning at 5 revolutions/second and falling from 15 m is 3680 N.

It is estimated that a squash ball travels at speeds of up to 120 mph (54 ms^{-1}).⁴ At this speed a squash ball weighing 25 g has a force of impact of 3645 N (Table

3), similar to the force of the baton. Both the end-stops of the baton and the squash ball can enter the orbit, but they are not directly comparable. The hard rubber of the end-stop transmits most of its force of impact to deforming the eye, while a large amount of the force of the squash ball is absorbed deforming the ball itself.

Thus baton twirling, a sport growing in popularity, has the potential to cause serious eye injury, especially in young people. The forces involved are similar to those in squash ball injuries, the dangers of which have been well documented.⁵ Eye protection, although recommended, is unlikely to be widely adopted. It is therefore important to be aware of the potential dangers of eye injury in this expanding sport. Interestingly, since this case the governing body of the sport has insisted on all competitors being insured against injury, particularly eye injury.

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Spontaneous hyphaema and corneal haemorrhage as complications of microbial keratitis

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SUMMARY Hyphaema developed spontaneously in 16 of 458 patients with microbial keratitis treated at two centres on the East and West Coasts of the United States. Chronic corneal conditions were often present, and three cases had rubeosis iridis. Inflamed iris vessels were assumed to be the source of the haemorrhage. The hyphaemas tended to persist longer than is usual, particularly when coincident with a hypopyon. Recurrent hyphaemas are reported in two patients from outside this series. Spontaneous corneal haemorrhage was seen in three cases. Subepithelial bleeding settled rapidly, but a combined midstromal and pre-Desemet's haematoma cleared more slowly. Anterior segment bleeding was significantly associated with advanced age, female sex, infection with Gram-positive organisms, and hypopyon.

Anterior segment haemorrhage is uncommon in the absence of trauma. Bleeding diatheses¹⁻⁴ or the rupture of pathological blood vessels are sometimes implicated. Bleeding may be caused by iris neovascularisation, as in diabetic rubeosis,⁵ or by abnormal tumour vessels in melanoma,⁶ retinoblastoma,⁷ or juvenile xanthogranuloma.⁷ Vascularised surgical wounds^{8,9} and iris neovascular tufts, occurring in proximity to the pupillary frill,^{10,11} have recently been described as causes of spontaneous hyphaema. Occlusive vasculitic processes¹² in, for example, herpetic uveitis or Stevens-Johnson syndrome, may also disrupt iris vessels. The spontaneous hyphaemas of Fuchs's uveitis syndrome¹³ probably arise from the iris rubeosis characteristic of this condition. Bleeding originating from presumably normal, if secondarily inflamed, iris vessels has not been reported.

Intracorneal haemorrhage¹⁴ has generally been described after surgery or incidental trauma; other associated conditions have included severe glaucoma and chemical burns.^{14,15}

We report the clinical findings and course of 16 patients with spontaneous hyphaema and three with corneal haemorrhage occurring in a large series of patients with suppurative inflammation of the cornea. Two illustrative case reports are included.

Subjects and methods

Bacterial keratitis was defined as an inflammatory infiltration and ulceration of the corneal stroma, associated with an epithelial defect, from which one or more bacterial or fungal species were cultured. The records of the patients were studied retrospectively at the University of Southern California (USC), Los Angeles, and at the Massachusetts Eye and Ear Infirmary, Boston. Standard microbiological techniques¹⁶ were used at both centres.

The inpatient and outpatient charts of 458 consecutive cases of microbial keratitis were examined by

Table 1 Prevalence data comparing microbial keratitis groups with and without haemorrhagic complications

Group	Age at presentation*				Total
	≤54 years		>54 years		
	Male	Female	Male	Female	
	No. (%)	No. (%)	No. (%)	No. (%)	
Patients with haemorrhagic complications	2 (1.3)	1 (1.3)	4 (3.5)	11 (9.6)	18
Patients without haemorrhage	152 (98.7)	74 (98.7)	111 (96.5)	103 (90.4)	440
Total	154	75	115	114	458

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*Data stratified round the median age of 54 years.

Table 2 Clinical characteristics of microbial keratitis patients with spontaneous hyphaema

Case	Age	Sex	Microbial aetiology	Ulcer size*	Predisposing causes	Other ocular conditions
1	28	M	<i>Staph. aureus</i>	M	Staple injury	—
2	78	F	<i>Staph. aureus</i>	M	Aphakia, extended-wear CL	—
3	87	F	<i>Staph. aureus</i>	M	Trauma, pseudophakia	—
4	78	F	<i>Staph. aureus</i>	M	Bullous keratopathy	Rubecotic glaucoma
5	68	F	Coagulase-negative staphylococcus	M	Bullous keratopathy	Granulomatous uveitis
6	69	M	Coagulase-negative staphylococcus	M	Zoster keratitis	—
7†	76	F	<i>Str. pneumoniae</i>	M	Bullous keratopathy	Rubecotic glaucoma
8	79	F	<i>Str. pneumoniae</i>	M	2 months post-PK	Postoperative glaucoma
9	81	M	<i>Str. pneumoniae</i>	M	—	—
10	63	M	β -streptococcus + β -streptococcus (2 types)	M	Assault	—
11	60	F	β -streptococcus	L	Table injury	—
12	73	F	<i>Pseudomonas aeruginosa</i>	L	Aphakia, daily-wear CL	—
13	58	M	<i>Pseudomonas aeruginosa</i>	S	Bullous keratopathy	Late-stage glaucoma
14	68	F	<i>Pseudomonas mesophilica</i>	M	Neurotrophic keratitis	—
15	62	F	NA	M	Bullous keratopathy	Rubecotic glaucoma
16	52	M	Culture negative	M	Tree branch injury	—

*S=small (<2 mm); M=moderate (2–6 mm); L=large (>6 mm). †Hyphaema and corneal haemorrhage developed concurrently. CL=Contact lens. PK=Penetrating keratoplasty. NA=Not available.

means of detailed protocols. The study population was distributed as follows: Los Angeles County-USC Medical Center (LAC-USC)—227 patients, 1972–1983; the Estelle Doheny Eye Foundation (EDEF), Los Angeles—55 patients, 1978–1984; and the Massachusetts Eye and Ear Infirmary (MEEI), Boston—176 patients, 1977–1981. Information was collected on several demographic and clinical variables including age, sex, duration of the condition, systemic and local predisposing factors, prior medications, features of the corneal ulcer, microbiological culture results, complications, and treatment. Patients with a spontaneous onset of hyphaema or intracorneal haemorrhage, occurring at presentation or during the treatment period, were selected for additional study. Two patients from outside the series are included for discussion.

Results

Of the 458 cases 16 developed a spontaneous hyphaema and three (including one combined with hyphaema) had intracorneal bleeding. Therefore during the acute stage of the inflammation approximately 4% of the patients had anterior segment haemorrhage.

The median age of the 458 patients was 54 years. The median age of the group with haemorrhagic

complications was 68.5 years (range 28 to 87 years). Twelve (67%) of the haemorrhagic group were female. Prevalence data for patients with and without haemorrhage are contrasted in Table 1. The patients with haemorrhagic complications were significantly older ($t=2.96$, with df 456; $p<0.005$) and more likely to be female ($\chi^2=5.05$, df 1; $p<0.05$) than the group without haemorrhage. Male patients developing haemorrhagic complications were on average 10 years older, and female patients were 14.5 years older, than their counterparts without such complications.

To explore whether women were at greater risk because they were older we stratified the patients by age, using the median (54 years) as an arbitrary cut-off point (Table 1). In the younger group there were twice as many men as women, and both sexes were equally likely to have haemorrhage into the anterior segment. The numbers of males and females over 54 years of age were equal, and the age distribution by decade was almost identical. The proportion of older patients with haemorrhage was significantly greater than that of younger patients ($\chi^2=8.32$, df 1; $p<0.01$). Older patients of both sexes were at higher risk than younger patients, but hyphaema or intracorneal bleeding developed in women nearly three times as often as in men in patients over 54 years old.

The clinical characteristics of the 16 patients with

(Table 2 continued)

Systemic conditions	Hypopyon	Prior topical steroids	Hyphaema coincident with S/C injections	Onset of hyphaema (days from admission)	Outcome
—	+	—	+	1	Small. Settled in 4 days
—	+	+	—	5	20% hyphaema. Layered. Slow to resolve
Diabetes	+	—	—	0	Small. Endophthalmitis developed
—	—	+	—	0	50% hyphaema. Organised. Enucleation day 27.
Warfarin (pulmonary embolism)	—	—	+	3	15% hyphaema. Settled in 1 week
—	+	+	—	12	10% hyphaema. Layered. Cleared in >2 weeks
—	+	—	+	4	30% hyphaema. Cleared in 2 weeks
—	+	+	+	5	Small. Settled in 5 days
Dementia	+	+	—	7	75% hyphaema. Layered. Slow to resolve. Late enucleation
Chronic alcoholism	—	—	—	0	25% hyphaema. Slow to resolve
Diabetes	+	—	—	12	Microhyphaema. Settled in 3 days
—	+	—	—	12	Small. Cleared rapidly
—	—	—	—	8	Small. Settled in 1 week
—	+	+	—	2	20% hyphaema. Intermixed with hypopyon. Slow to resolve
—	+	—	—	0	10% hyphaema. Intermixed with hypopyon. Enucleated
—	+	—	—	3	Small. Intermixed with hypopyon. Settled in 6 days

spontaneous hyphaema are shown in Table 2 and of the three patients with corneal haemorrhage in Table 3. Late hyphaemas developed in five traumatised eyes (patients 1, 3, 10, 11, 16), all following the onset of corneal infection. Both hyphaema and corneal haemorrhage developed spontaneously in one patient (case 7).

The microbial keratitis involved Gram-positive organisms in 13 of the 16 culture-positive cases. Hypopyon was twice as prevalent in patients with spontaneous haemorrhage into the anterior segment (13 of 18) as in patients in the overall series (149 of 440) without bleeding ($\chi^2=11.1$, df 1; $p<0.001$).

The two subepithelial corneal haemorrhages cleared rapidly, but the midstromal and pre-Desemet's haematoma (case 7), associated with hyphaema, cleared much more slowly. Blood staining or other sequelae were not noted, and corneal bleeding did not pose a significant problem in this series.

The bleeding site was not seen in any patient; the conditions of microbial keratitis inhibit fine observation of the iris and anterior chamber. Iris neovascular tufts were not reported. Secondary bleeding, glaucoma (apart from the four cases with premorbid glaucoma), and corneal blood staining were not observed. However, we have recently seen two patients with major complications of hyphaema not observed in this series; their case reports follow.

CASE A

A 65-year-old South African black male developed a moderate-size paracentral *Streptococcus viridans* microbial keratitis. Several days later, at admission, he had a 10% hyphaema, without hypopyon, and was treated with subconjunctival injections of cephalothin and gentamicin and with topical chloramphenicol. The corneal infection improved rapidly, but on day 4 after admission secondary bleeding into the anterior chamber and a 50% hyphaema developed. Resolution occurred over a period of three weeks. There were no permanent sequelae.

CASE B

A 72-year-old male was treated at Massachusetts Eye and Ear Infirmary for a moderate-size suppurative corneal ulcer caused by a *Klebsiella oxytoca* infection of a herpes simplex trophic ulcer. When admitted, he had a 50% hyphaema, without hypopyon, and an intraocular pressure of 42 mmHg. He was treated with frequent high-dose topical cephazolin and gentamicin eye drops. Despite a rapid improvement of the keratitis the hyphaema increased to fill most of the anterior segment, and early corneal blood staining was noted on day 5. Three anterior chamber irrigations were performed over the next two weeks, each followed by severe bleeding. The intraocular pressure remained at 40 mmHg for nearly one month despite maximal glaucoma therapy. Ultimately the

Table 3 Clinical characteristics of microbial keratitis patients with intracorneal haemorrhage

Case	Age	Sex	Microbial Aetiology	Ulcer size*	Predisposing causes	Other ocular conditions	Systemic conditions
7†	76	F	<i>Str. pneumoniae</i>	M	Bullous keratopathy	Rubecotic glaucoma	—
17	78	F	Coagulase-negative staphylococcus	M	Zoster keratouveitis	—	Chronic lymphatic leukaemia
18	49	F	α -streptococcus + coagulase-negative staphylococcus + <i>Enterococcus</i> spp.	L	Dry eye	—	Chronic alcoholism

*S=small (<2 mm); M=moderate (2–6 mm); L=large (>6 mm). †Hyphaema and corneal haemorrhage developed concurrently. SC=subconjunctival.

ocular hypertension cleared and the hyphaema resolved slowly. The patient died before long-term sequelae could be assessed.

Discussion

Haemorrhagic complications of microbial keratitis are uncommon. They occurred in 4% of 458 patients in this series and also in 4% (6 of 140) of patients with microbial keratitis admitted to St Johns Hospital, Soweto, South Africa, in March 1981–February 1982 (unpublished data). The aetiology of the bleeding appeared to be multifactorial. Advancing age was a significant prognostic factor in both men and women. The risk of anterior segment bleeding was also two to three times greater for women than for men in the older age groups. These findings, however, are based on a relatively small number of patients. The preponderance of Gram-positive bacteria and the remarkably high prevalence of hypopyon (72%) suggest that the microbial infection involved strains of moderate virulence but high phlogogenicity. Bacterial proteases, cytolytic toxins, and streptokinases might play an important part in causing haemorrhage.

Two-thirds of the patients had local ocular predisposing factors (besides trauma), some of which may have been associated with chronic anterior segment inflammation. Prior treatment with topical steroids in six patients may also have contributed to the intraocular bleeding by increasing local vascular fragility. Trauma associated with subconjunctival injections appeared unrelated. Three patients presumably bled from pre-existing iris rubeosis (thrombotic glaucoma), and hyphaema developed spontaneously in one patient when long-term warfarin therapy was complicated by the advent of microbial keratitis. Two patients were chronic alcoholics and one patient had chronic lymphatic leukaemia, but all three had normal haemostatic profiles.

Spontaneous hyphaema has been reported as a complication of severe vasculitic uveitis,^{12,17,18} but not following microbial keratitis. An important observation is that the course of hyphaema complicating microbial keratitis often differs from that of traumatic hyphaema.¹⁹ Early bleeding mixed with the hypopyon to variable degrees; later haemorrhage layered over the hypopyon. In three eyes the bleeding filled >25% of the anterior chamber. Further bleeding did not occur in this series, but was seen in two other patients (cases A and B). In case B corneal blood staining and a prolonged pressure rise were major problems. In several cases the resorption of the blood and hypopyon was unduly prolonged.

The available follow-up was insufficient to provide an adequate analysis of the long-term sequelae of haemorrhage in these severely inflamed eyes, as distinct from those caused by the inflammatory process itself. Retention of blood in the anterior chamber can lead to fibrovascular organisation, posterior and peripheral anterior synechiae formation, corneal blood staining, glaucoma, and optic atrophy.¹⁹ The frequently prolonged natural history of hyphaema in these inflamed eyes suggests that intraocular bleeding is a potentially serious complication of microbial keratitis, as illustrated in case B.

When spontaneous hyphaema has occurred, mydriasis may tamponade irideal vessels and control bleeding.¹¹ It may sometimes be possible to photo-coagulate the bleeding site with argon laser, as suggested for iris neovascular tufts.²⁰ Aspirin therapy should be stopped³ and the haemostatic status investigated.¹ The intraocular pressure must be closely monitored. After the corneal infection is controlled, topical steroids may be beneficial in reducing the inflammation.¹⁹

Duke-Elder and Leigh²¹ noted that corneal haemorrhage almost invariably occurs from areas of neovascularisation, particularly following interstitial and mustard gas keratitis. There are several isolated

Hypopyon	Prior topical steroids	Corneal haemorrhage coincident with SC injections	Onset of corneal haemorrhage (days from admission)	Corneal site	Outcome
+	—	—	4	Midstromal and pre-Descemet's membrane	Still present at 1 month
+	—	+	2	Subepithelial	Cleared rapidly
—	—	—	22	Subepithelial	Cleared over 1 week

reports of corneal haemorrhage complicating microbial keratitis.²²⁻²⁴ Muenzler believes that haemorrhages may not be uncommon in the vascularised cornea and may go unnoticed because of their usually small size and limited duration.¹⁴ Large, superficial corneal haemorrhages may be drained by removing the overlying epithelium with a moist cotton-tipped applicator.²⁵ Deep corneal haemorrhages may, however, require formal surgical drainage^{26,27} because of their tendency to occlude the drainage angle, their chronicity,²⁸ and organisation with scarring.

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Ophthalmic emergencies in a district general hospital casualty department

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SUMMARY A survey of ophthalmic emergencies attending the casualty department of a district general hospital over a 12-month period is presented. The total number of new casualty attendances was 30 649 of which 1870 (6.1%) presented with an ophthalmic problem. There was a 3 to 1 male to female preponderance and a peak age of presentation between 20 and 30 years. The main aetiological factors were trauma 65.6% and inflammation 21.7%. Of the trauma patients 80% had sustained minor trauma (abrasions or foreign material to the cornea or conjunctiva) and of the patients with inflammation 71% had either conjunctivitis or blepharitis. There was a trend towards increased numbers in the summer months. The percentage of patients with inflammatory disease was higher in the early summer and the winter months. Nine of the 11 patients with acute angle closure glaucoma presented between November and February. All patients were initially seen by the accident and emergency medical staff, who were able to treat 69% without further consultation. No serious pathology was overlooked. It is suggested that, in the district general hospital setting, co-operation between the eye and the accident and emergency departments can be to their mutual benefit.

The problem of ophthalmic emergencies and their management has been the subject of three recent papers,¹⁻³ all of which have been based on data collected from specialist eye emergency units. Opinion as to the role of the doctor and the nurse has varied. This study aims to assess the ophthalmic workload of an accident and emergency (A and E) department in a district general hospital (DGH) where all patients attending are seen in the first instance by A and E medical staff with basic ophthalmic training and then referred where necessary to the ophthalmic resident or to the eye clinic.

The results are presented to give an insight into the handling of eye emergencies in the A and E department, the variety and frequency of the presenting conditions, and their seasonal variation. The benefits and pitfalls of an ophthalmic emergency service run in conjunction with a general emergency service are discussed.

Material and methods

The Accident and Emergency department of the Kent and Canterbury Hospital provides a 24-hour
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service for all specialties in the Canterbury and Thanet Health District (population 288 100)⁴ though many casualties from the Thanet towns (population approximately 130 000) can attend a casualty department at Margate between 8 am and 12 pm, and some casualties from Deal, Dover, and Folkestone travel to Canterbury rather than to Ashford (the only other hospital with a 24-hour casualty service in East Kent). The Kent and Canterbury Hospital is, however, the only hospital in East Kent (Canterbury and Thanet and South East Kent Health Districts (population 546 600)⁴ which provides a specialist ophthalmic emergency service, one room in the A and E department containing a slit-lamp, vision testing chart, and the equipment necessary for basic eye examination and treatment. All patients undergo an examination by A and E medical staff trained in basic eye examination and the use of the slit-lamp by one of the ophthalmic consultants. The patient is then treated by that doctor or referred to the on-call ophthalmic resident, who will then either complete the initial treatment and arrange follow-up if necessary or refer to the on-call consultant. Except in a few cases of minor trauma, follow-up is generally completed in the general ophthalmic clinic, but fresh

instruction of A and E medical staff by the ophthalmic staff and feedback of information are a continuing process.

The attendance of eye casualties at the A & E department over the 12 month period May 1983 to April 1984 inclusive was studied. Eye emergencies referred directly by the general practitioner to the general ophthalmic clinics were not included in the study. The numbers of patients attending with an eye problem were collected prospectively. At the end of that period casualty and inpatient records were analysed retrospectively. Detailed information about each patient was recorded, including date of attendance, place of residence, method of referral, principal diagnosis, designation of doctor seeing the patient, and disposal.

A diagnostic index of all expected diagnoses was drawn up. Diagnoses were then broadly grouped into

traumatic (the injured eye), inflammatory (the red eye), degenerative (mainly vascular and vitreoretinal problems), and miscellaneous. A detailed breakdown of these groups was then made.

When a patient had more than one diagnosis, only the most serious diagnosis was listed.

Results

A total of 1957 visits were made for eye complaints. Of these, 1870 were for new complaints or new episodes of illness. They composed 6.1% of the 30 649 total of new patients for all specialties visiting the department during this time (Table 1).

Trauma (1228 patients) accounted for almost two-thirds (65.6%) of the total caseload (Table 2), and 985 cases (80.2% of this group) fell into the category of minor trauma (abrasions and foreign bodies to the

Table 1 Numbers and ages of patients attending

Age in years	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total numbers
0-9	3	4	4	13	15	23	11	13	13	7	5	8	119 (6.4%)
10-19	20	27	19	25	23	26	36	20	20	29	28	19	292 (15.6%)
20-29	48	26	34	28	41	37	47	48	37	46	50	27	469 (25.1%)
30-39	29	30	40	38	33	32	45	35	32	33	26	26	399 (21.3%)
40-49	24	21	16	27	19	19	17	20	30	27	20	19	259 (13.9%)
50-59	18	8	14	13	12	16	14	10	13	10	14	14	156 (8.3%)
60-69	6	5	2	7	9	8	6	7	5	14	4	6	79 (4.2%)
70-79	5	5	6	4	10	2	6	4	5	5	3	5	60 (3.2%)
80-89	2	—	—	4	—	2	—	—	2	—	2	3	15 (0.8%)
90-99	—	—	—	—	—	—	—	—	—	—	1	—	1 (<0.1%)
Not known	—	—	2	3	2	1	5	4	1	1	1	1	21 (1.1%)
Total	155	126	137	162	164	166	187	161	158	172	154	128	1870

Table 2 Main diagnostic categories

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
Trauma	95 (61.3)	87 (69)	101 (73)	110 (67.9)	98 (59.7)	98 (59)	120 (64.4)	115 (71.4)	99 (62.7)	121 (70.3)	105 (68.2)	79 (61.7)	1228 (65.6)
Inflammation	40 (25.8)	24 (19.0)	22 (16.1)	33 (20.3)	42 (25.6)	50 (30.1)	48 (25.7)	24 (14.9)	31 (19.6)	28 (16.2)	34 (22)	30 (23.4)	405 (21.6)
Degenerative	6 (3.9)	4 (3.2)	2 (1.5)	4 (2.5)	11 (6.7)	7 (4.2)	7 (3.7)	5 (3.1)	8 (5.1)	11 (6.4)	5 (3.2)	5 (3.9)	75 (4.0)
Miscellaneous	14 (9)	11 (8.7)	12 (8.8)	15 (9.25)	13 (7.9)	11 (6.6)	12 (6.4)	17 (10.6)	20 (12.7)	12 (7.0)	10 (6.5)	14 (10.9)	162 (8.7)
Total	155	126	137	162	164	166	187	161	158	172	154	128	1870

Percentages in parentheses.

Table 3 Analysis of trauma cases (1228 cases)

Diagnosis	Number	Percent	Diagnosis	Number	Percent
Corneal foreign body	405	33.0	Hyphaema	28	2.2
Corneal abrasion or non-penetrating laceration	229	24.3	Lid laceration	26	2.1
Conjunctival or sub tarsal foreign body	162	13.2	Traumatic uveitis/mydriasis	16	1.3
Chemicals in eye	89	7.2	Thermal burns	12	1.0
Radiational (mainly welding flash)	64	5.2	Perforating injury	11	0.9
Contusion (black eye)	59	4.8	Traumatic vitreous haemorrhage	2	<0.1
Minor trauma to conjunctiva	55	4.5			

Table 4 Seasonal variations for certain diagnoses

Condition	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec
Trauma												
Corneal foreign body	33	32	32	32	34	33	39	39	32	46	43	18
Corneal abrasion	25	19	29	25	26	17	42	23	23	21	27	22
Hyphaema	6	1	2	6	2	1	1	5	1	—	1	2
Inflammations												
Conjunctivitis	18	15	14	10	19	16	15	6	14	18	16	14
Allergy	3	—	3	2	9	18	10	7	7	3	—	1
Iritis	5	2	—	5	3	7	11	4	2	—	4	1
Acute glaucoma	2	1	—	1	—	—	1	—	—	—	1	5

Table 5 Analysis of inflammation cases (406 cases)

Diagnosis	Number	Percent
Conjunctivitis	175	43.2
Allergy	63	15.5
Lid inflammation	51	12.6
Keratitis	47	11.6
Iritis	44	10.9
Acute glaucoma	11	2.7
Scleritis/episcleritis	6	1.5
Orbital cellulitis	5	1.2
Herpes zoster ophthalmicus	4	1.0

cornea or conjunctiva) (Table 3). The commonest serious problem was hyphaema (28 patients), accounting for 2.2% of the total. Eighty seven patients (7.2%) attended with chemical spillage into the eye, but the majority were relatively innocuous (most commonly shampoo or hair spray), and only four patients in this group required hospital admission. Thirty six patients had problems associated with contact lens wear.

None of the main categories of trauma showed any seasonal variation (Table 4), and although the number rose in the summer months proportions in relation to other diagnoses did not.

Inflammatory conditions (406 patients) accounted for 21.7% of the total caseload (Table 5). Conjunctivitis, blepharitis, and allergy were the diagnoses for 287 (70.7%) patients.

The percentage of patients with inflammatory conditions (Table 2) was higher in November to January and May to July but lower in February to April and August to October. Allergic conditions were most frequent during the summer months (Table 5), reaching a peak of 18 cases in June compared with none in February. Twenty six (59%)

cases of iritis occurred between the months of April and July, and nine of the 11 patients with acute glaucoma presented between November and February.

Of patients with 'miscellaneous conditions' (8.7% total) 51% attended without symptoms or signs of eye disease but to seek reassurance following minor trauma.

One hundred and twenty-four patients (6.6%) required admission to hospital (Table 6), the two commonest diagnoses being hyphaema and retinal tear/detachment. Inspection of inpatient records showed that any cases admitted had seen the ophthalmic resident or been referred straight to the eye clinic immediately prior to admission. No patient requiring admission had been discharged from the A and E department.

Of the 1870 new cases 1667 (89.7%) were self referrals; 1715 (91.7%) resided in East Kent. The numbers from outside the catchment area were greater in the summer months but none the less small (15 in August compared with four in February), indicating that in East Kent at least the impact of holiday visitors on the ophthalmic emergency service was slight. There was a 3 to 1 male to female preponderance—1410 males (75%) to 470 females (25%). The peak age for attendance was 20–29 years. The numbers of patients attending showed an increase in the summer months, but the only age group to show a marked seasonal change was the 0–9 age range where numbers varied from three in January to 23 in June, the commonest diagnosis in this group being allergic oedema of the lids and conjunctiva.

Follow-up visits to the A and E department were made by 87 patients; 65 (75%) were arranged by the

Table 6 Diagnosis for 124 patients requiring admission

Hyphaema	28 (22.5%)	Deep corneal foreign body	9 (7.3%)
Retinal tear/detachment	13 (10.5%)	Other blunt injury	7 (5.6%)
Acute glaucoma	11 (8.9%)	Non-penetrating corneal laceration	5 (4%)
Perforating injury	11 (8.9%)	Herpes zoster ophthalmicus	4 (3.2%)
Vitreous haemorrhage	10 (8.1%)	Chemical burn	4 (3.2%)
Keratitis	9 (7.3%)	Others (including uveitis, cellulitis, orbital fractures)	13 (10.5%)

Table 7 Disposal of 1870 new cases seen by Accident and Emergency medical staff

Disposal	Number	Percent
Discharged	1289	68.9
Direct referral to ophthalmic resident	314	16.8
Follow-up appointment in general ophthalmic clinic	202	10.8
Follow-up appointment in A and E Department	65	3.5

A and E medical staff and 22 (25%) were patients referring themselves back. Of the patients booked for follow-up 86% had minor trauma, but 41% of the self referrals were for unresolved minor inflammatory problems. Two cases of conjunctivitis later found to be iritis had been referred back by the A and E medical staff for follow up.

Much of the ophthalmic emergency work was done by the A and E medical staff (Table 7) who made the initial assessment of all the new cases. Of these patients, 1556 (83%) were assessed, the initial decisions were made, and management was undertaken by the A and E medical staff without calling ophthalmic staff to the department. However, 224 of these 1556 were referred to the Eye Clinic either immediately after the initial consultation or following a return visit. Thus a total of 1332 cases (71.2% of the 1870 new attenders) were managed solely by the A and E department and 538 cases (28.8%) required review by the Eye Department either immediately (314 cases) or at outpatient follow-up (224 cases).

Discussion

This study is the first of its kind from a district general hospital. The population was from small towns and rural areas with no inner city catchment area. The studies from Bristol, Southampton, and Leicester were from specialist eye departments based on teaching hospitals in large cities. However, a number of common factors emerge. All studies show a male preponderance of between 2:1 and 3:1, and where the age of the patient is noted the commonest age of presentation is the 3rd decade.

Of the patients presenting with trauma, minor conjunctival and corneal trauma including foreign bodies accounted for between 82 and 93% of patients, and minor conjunctival and lid inflammation for between 67 and 80% of patients, presenting with inflammatory disorders.

In this study almost 90% of patients were self-referred, a similar experience to that of Bristol and Southampton, whereas the number was only 56% from Leicester (30% were referred via general practitioners). This difference may be due to their

casualty department being located in the general eye clinic.

This probably explains why 65.6% of our patients presented with minor trauma and only 21.7% with inflammatory disorders compared with between 43 and 52% for trauma and 29 and 45% for inflammatory disorders in the other centres: an episode of inflammatory disease was more likely to become recurrent or chronic and demand repeated attendances than a single incident of minor trauma.

Other differences in results may be related to the extent to which the casualty departments provide a comprehensive eye service. In East Kent patients with chronic or recurrent problems are usually referred by their general practitioner straight to the general eye clinic in a separate location from the A and E Department.

Although the case load in this study is predominantly minor trauma and inflammatory conditions, there is in common with other studies a large spread of diagnoses, many of which require careful evaluation. The one diagnosis missing from this study taken after the passing of the seat belt laws is perforating injury caused by a car windscreen.

This study attempted to evaluate seasonal factors in the presentation of ophthalmic emergencies. Although there is a trend towards higher numbers in the summer, it does not reach statistical significance. The numbers of patients with all types of trauma showed little fluctuation with the seasons. This may be due to their being mainly related to year-round activities, such as work occupation, house repairs, and car repairs, though no detailed study of the circumstances of the injury was made.

Inflammatory eye disease in general made up a greater percentage of the case load in the early summer months and the winter months, with higher percentages in November to January and May to July. The summer peak may be reflected in the high incidence of allergies and iritis during these months, and the winter peak may be due to the higher incidence of upper respiratory tract infections and associated conjunctivitis. The incidence of acute angle closure glaucoma was also higher in the winter months (a well known association).

A further aim of this study was to contribute towards the debate about who sees an ophthalmic emergency. It is generally agreed that this is a primary care function, and yet the majority of patients constituting ophthalmic emergencies refer themselves to hospitals rather than their general practitioner, a pattern which seems unlikely to change unless individual general practitioners in group practice develop a special interest in ophthalmology. Morell² states that only 1.6% of his consultations were for ophthalmic problems. Yet patients

with ophthalmic problems accounted for 6.1% of the patients attending this A and E Department. While the A and E case load and the general practitioners' caseload are not identical, it seems likely that the proportion of ophthalmic consultations in general practice may be higher away from the large cities with dedicated ophthalmic emergency departments.

The studies so far show that most ophthalmic emergencies are minor in nature and treatable by personnel without extensive specialist training in ophthalmology. In Southampton 57.1% of patients first saw an ophthalmic trained nurse.

Not all hospitals with ophthalmic departments have the numbers of staff and the facilities to run a separate emergency service dedicated to ophthalmology, but where there is an A and E department a useful ophthalmic service can be provided.

In this study all the patients were initially seen by the A and E medical staff, and 69% were discharged from the department after only one consultation with the A and E doctor. Although few patients were seen again in the department, the majority of those brought back for follow-up were also discharged. In no case was serious pathology missed and in no case was hospital admission unduly delayed.

However, this system needs safeguards to be efficient and safe. It requires the provision of equipment, including a slit-lamp necessary for eye examination. It requires that an ophthalmology opinion be

quickly available and it requires initial training of A and E medical staff in the use of the slit-lamp and removal of foreign material from the eye. There should also be co-operation and feedback between the ophthalmology and the A and E departments. This system can then be mutually beneficial to both departments, sparing the ophthalmic department the work of assessing and treating many minor problems and providing ophthalmic experience likely to be encountered in general practice for the A and E residents, many of whom may later enter this field.

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